IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Patrick L. COLEMAN et al.
Group Art Unit: 1637

Serial No.: 09/819,317
Examiner: J. N. Fredman
Confirmation No.: 4377
Filed: 28 March 2001
Docket No.: 56066US002

Title: METHOD OF TRANSFERRING MOLECULES TO A FILM LAMINATE

Assistant Commissioner for Patents
Washington, D.C. 20231

We are transmitting the following documents along with this Transmittal Sheet (which is submitted in triplicate):

X An itemized return postcard.
___ A Petition for Extension of Time for __ month(s) and a check in the amount of $___ for the required fee.
___ An Information Disclosure Statement (__ pgs); copies of ___ applications; 1449 forms (___ pgs); and copies of ___ documents cited on the 1449 forms.
X Please charge Deposit Account No. 13-4895 in the amount of $320.00, for filing a Brief in support of an Appeal.
___ A certified copy of a __ application, Serial No. __, filed _____, the right of priority of which is claimed under 35 U.S.C. §119.
X Other: Appellants' Brief on Appeal (in triplicate) (192 pgs total - including Appendices I-VIII (184 pgs)).
___ Amendment ___ No Additional fee is required. ___ The fee has been calculated as shown:

Fee Calculation for Claims Pending After Amendment

	Pending Claims after Amendment (1)	Claims Paid for Earlier (2)	Number of Additional Claims (1-2)	Cost per Additional Claim	Additional Fees Required
Total Claims				x $18 =	
Independent Claims				x $84 =	
One or More New Multiple Dependent Claims Presented? If Yes, Add $280 Here →					
Total Additional Claim Fees Required					

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 13-4895. Triplicate copies of this sheet are enclosed.

MUETING, RAASCH & GEBHARDT, P.A.

By: _____
Name: Loren D. Albin
Reg. No.: 37,763
Direct Dial: 612-305-1225
Facsimile: 612-305-1228

CERTIFICATE UNDER 37 CFR §1.10::
"Express Mail" mailing label number: EV 073 735 612 US
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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

By: _____
Name: Loren D. Albin

(LARGE ENTITY TRANSMITTAL UNDER RULE 1.10)

PATENT
Docket No. 56066US002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	Patrick L. COLEMAN et al.	Group Art Unit:	1637
Serial No.:	09/819,317	Examiner:	J. N. Fredman
Confirmation No.:	4377		
Filed:	March 28, 2001		

For: METHOD OF TRANSFERRING MOLECULES TO A FILM LAMINATE

APPELLANTS' BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

This Brief is presented in support of the Appeal filed February 28, 2003, from the final rejection of claims 1, 3-11, 23, and 26 of the above-identified application under 35 U.S.C. §103(a), as set forth in the Final Office Action mailed October 30, 2002 and the Advisory Action mailed February 5, 2003.

This Brief is being submitted in triplicate, as set forth in 37 C.F.R. §1.192(a). Please charge Deposit Account No. 13-4895 the fee for filing this Brief under 37 C.F.R. §1.17(f).

I. REAL PARTY IN INTEREST

The real party in interest of the above-identified patent application is the assignee, 3M Innovative Properties Company.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to Appellants' Representatives which would directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The pending claims are claims 1, 3-11, 23, and 26 are listed in Appendix I. Claims 1, 3-11, 23, and 26, which are the subject of this appeal, stand rejected under 35 U.S.C. §103(a).

IV. STATUS OF AMENDMENTS

The Examiner issued a nonfinal Office Action mailed June 10, 2002 (Appendix II). A Restriction Requirement was issued setting forth the following inventions: Group I, claims 1-11 and 16-25; and Group II, claims 12-15. Appellants elected Group I without traverse. Further, claims 1-5, 7-11, 16-21, and 23-25 were rejected under 35 U.S.C. §102(b). Finally, claims 6 and 22 were rejected under 35 U.S.C. §103(a).

Appellants filed an Amendment and Response filed September 10, 2002 (Appendix III), in which claims 2, 16-22, and 24-25 were canceled, claims 1, 3, and 23 were amended, and the rejections were traversed.

The Examiner issued a final Office Action mailed October 30, 2002 (Appendix IV), in which the rejection under 35 U.S.C. §102 was withdrawn, and claims 1, 3-11, 23, and 26 were rejected under 35 U.S.C. §103(a).

Appellants filed an Amendment and Response Under 37 C.F.R. §1.116 filed January 29, 2003 (Appendix V), in which claims 12-15 were cancelled and claim 26 was amended to correct a typographical error.

The Examiner issued an Advisory Action mailed February 5, 2003 (Appendix VI), indicating that the proposed amendments were not entered, but that they would be entered for the purposes of Appeal, wherein claims 1, 3-11, 23, and 26 would stand rejected under 35 U.S.C. §103(a). Thus, the clean copy of the claims listed in Appendix I represent the claims as amended (including the amendment to claim 26).

Appellants Representative, Loren D. Albin, conducted a telephonic interview with Examiner Jeffrey Fredman on February 24, 2003 to discuss arguments for the patentability of Appellants claimed invention. However, no agreement was reached as to the patentability of the rejected claims.

V. SUMMARY OF THE INVENTION

Appellants' presently disclosed invention relates to a method of transferring molecules positioned within a matrix to a laminate (e.g., claims 1, 3-11, 23, and 26). Notably, the specification (e.g., page 5, lines 15-25) describes a matrix as follows:

> The matrix of the claimed method can be any matrix suitable for separating molecules. Such separation can be based on differences in the size, shape, electrical charge or any other physical or chemical property of the molecules that can be the basis for separating molecules from one another in a mixture. As nonlimiting examples, agarose gels are known to be useful for separating polynucleotides and polyacrylamide gradient gels containing sodium dodecyl sulfate (SDS) are known to be useful for separating polypeptides, e.g., proteins. The matrix may be of uniform concentration throughout, such as a 1% agarose, which may be used to separate polynucleotides. Alternatively, the matrix may be a gradient, such as a 4-15% SDS-polyacrylamide gel for the separation of proteins. Other possible types of gels are known and may be used for the claimed method. One of skill in the art will be able to select a matrix appropriate for any desired application.

The method includes: (a) providing a laminate including i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area, and ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel including linking agents; (b) contacting the matrix with the laminate; (c) transferring molecules from the matrix to the laminate; (d) removing the matrix from the laminate; and (e) shrinking the laminate so that the topographical surface area is greater than the projected surface area (e.g., claims 1, 3-11, 23, and 26).

VI. ISSUE(S) PRESENTED FOR REVIEW

Whether the Examiner has presented a *prima facie* case of obviousness under 35 U.S.C. §103(a) for claims 1, 3-11, 23, and 26 being unpatentable over PCT International Publication No. WO 99/53319 (Halverson et al.) in view of U.S. Patent No. 4,589,965 (Kreisher et al.).

VII. GROUPING OF CLAIMS

For the purpose of this appeal, claims 1, 3-11, 23, and 26 stand or fall together.

VIII. ARGUMENT

THE EXAMINER HAS FAILED TO ESTABLISH THE NECESSARY MOTIVATION FOR COMBINING THE DOCUMENTS AND A REASONABLE EXPECTATION OF SUCCESS

"To establish a *prima facie* case of obviousness . . . [f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference

teachings. Second, there must be a reasonable expectation of success. . . . The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. §706.02(j). *See also*, *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); and *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) (reversing "the Examiner's conclusion that it would have been obvious to substitute the Warnick nitric oxide detector for the Eads sulfur dioxide detector in the Eads system").

Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for at least the reasons discussed herein below.

A. *The Disclosure of Halverson et al.*

Halverson et al. disclose high-density miniaturized arrays and methods of manufacturing high-density miniaturized arrays. The methods of making the arrays include affixing one or more reactants directly to the array substrate by spotting, as exemplified in Example 4 using a capillary tube and in Example 5 using an aluminum post. As acknowledged by the Examiner, Halverson et al. lack specific disclosures of transferring *molecules positioned within a matrix*, contacting *the matrix with the laminate*, transferring molecules *from the matrix to the laminate*, and removing *the matrix from the laminate*.

B. *The Disclosure of Kreisher et al.*

Kreisher et al. disclose a method of electroblotting molecules from a gel to a blot membrane:

> The electrophoretically resolved material in the gelatin sheet is placed in contacting relationship with an immobilizing material. *Any suitable immobilizing material* can be used, such as membranes, papers, nylon, nitrocellulose,

> diazobenzyloxymethyl (DBM) paper, diazophenylthioether (DPT) paper, and the like.

(Column 4, lines 5-10, emphasis added). Thus, Appellants' respectfully submit that one of skill in the art would recognize that Kreisher et al. disclose that *porous* materials (e.g., membranes and papers) are suitable as immobilizing materials.

However, Kreisher et al. lack, among other things, a disclosure of (1) a laminate including i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area, and ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel including linking agents, and (2) shrinking the laminate so that the topographical surface area is greater than the projected surface area.

As discussed herein below, Appellants respectfully submit that, absent Appellants' present disclosure, it would *not be obvious* to one of skill in the art that the laminate disclosed by Halverson et al. would be a *suitable immobilizing material* for use in the method of electroblotting disclosed by Kreisher et al.

C. *One of Skill in the Art Would Have No Reasonable Expectation of Success in Using an Array Substrate of Halverson et al. as an Immobilizing Material in the Electroblotting Method of Kreisher et al.*

One of skill in the art might arguably have a reasonable expectation of success in using a *porous* material (e.g., a membrane or paper) as an immobilizing material in the electroblotting method of Kreisher et al. However, Halverson et al. not only fail to specifically disclose an array substrate that is a porous material, they in fact *teach away* from an array substrate that is a porous material by suggesting that the array includes a substrate that provides a preferably *non-porous* surface (e.g., page 8, lines 34-35). "A prior art reference must be

considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. §2141.03 (emphasis in original), citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

Thus, absent Appellants' present disclosure, one of skill in the art would have no motivation to use an array as disclosed by Halverson et al. as an immobilizing material in the electroblotting method of Kreisher et al., with a reasonable expectation of success.

D. *The Art of Record Fails to Suggest the Desirability of the Combination*

"The mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. §2143.01 (emphasis in original), citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

As discussed herein above, Halverson et al. disclose high-density miniaturized arrays, but they fail to specifically suggest the desirability of transferring molecules positioned within a matrix to their substrate.

Further, as discussed herein above, Kreisher et al. disclose a method of electroblotting molecules from a gel to a blot membrane, but they fail to suggest the desirability of using substrates, as disclosed by Halverson et al., as immobilizing materials suitable for use in electroblotting.

Thus, the art of record fails to suggest the desirability of the combination of Halverson et al. and Kreisher et al.

E. *Summary*

For the many foregoing reasons, it is respectfully submitted that *prima facie* case of obviousness has not been established. It is earnestly requested that the Board reverse the Examiner's rejections, and that all of the claims be allowed.

Respectfully submitted,

Patrick L. COLEMAN et al.,

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
(612)305-1220

April 28, 2003
Date

By: _____
Loren D. Albin
Reg. No. 37,763
Direct Dial: (612) 305-1225

LDA/rgg

CERTIFICATE UNDER 37 CFR §1.10:

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Date of Deposit: April 28, 2003

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By: _____
Name: Loren D. Albin

APPENDIX I.

Serial No.: 09/819,317

Docket No.: 56066US002

Claims 1, 3-11, 23, and 26 are provided below.

1. A method of transferring molecules positioned within a matrix to a laminate comprising:

(a) providing a laminate comprising

i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area, and

ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel comprising linking agents;

(b) contacting the matrix with the laminate;

(c) transferring molecules from the matrix to the laminate;

(d) removing the matrix from the laminate; and

(e) shrinking the laminate so that the topographical surface area is greater than the projected surface area.

3. The method of claim 1 wherein the linking agents comprise azlactone copolymers.

4. The method of claim 1 wherein the laminate further comprises a mask layer.

5. The method of claim 4 wherein the mask layer is in direct contact with the substrate and underlies the hydrogel.

6. The method of claim 1 wherein the one or more molecules are transferred from the matrix to the laminate by electroblotting.

7. The method of claim 1 wherein the matrix contains polynucleotides, polypeptides, polysaccharides, or combinations thereof.

8. The method of claim 1 wherein the matrix comprises an agarose gel or a polyacrylamide gel.

9. The method of claim 1 further comprising detecting the one or more molecules transferred from the matrix to the laminate.

10. The method of claim 1 wherein the shrinkable polymeric film is flexible.

11. The method of claim 1 wherein the shrinkable polymeric film is heat-shrinkable.

23. The method of claim 1 wherein the molecules comprise polynucleotides, polypeptides, polysaccharides, or combinations thereof.

26. The method of claim 1 wherein the step of transferring molecules from the matrix to the laminate comprises forming covalent bonds between at least a portion of the molecules and the linking agents.

APPENDIX II.

Serial No.: 09/819,317

Docket No.: 56066US002

Non-final Office Action mailed from the U.S. Patent and Trademark Office on June 10, 2002.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,317	03/28/2001	Patrick L. Coleman	56066~~USA1A.002~~ US002	4377

7590 06/10/2002

Attention: Christopher D. Gram
Office of Intellectual Property Counsel
3M Innovative Properties Company
P.O. Box 33427
St. Paul, MN 55133-3427

EXAMINER
MAUPIN, CHRISTINE L

ART UNIT	PAPER NUMBER
1637	3

DATE MAILED: 06/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,317	COLEMAN ET AL.	
	Examiner	Art Unit	
	Christine L. Maupin	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *12-15* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-11, and 16-25, drawn to a method of transferring molecule to a laminate, classified in class 430, subclass 53.

II. Claims 12-15, drawn to a composition of film laminates, classified in class 427, subclass 2.13.

The inventions are distinct, each from the other because of the following reasons:

Inventions of group II and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the composition of group II may be made by Langmuir-Blodgett methods combined with gel transfer, SDS-polyacrylamide gel synthesis, or by synthetic reactions driven by an electro current.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Gram on 7 May 2002 a provisional election was made without traverse to prosecute the invention of group I, claims 1-11, and 16-25. Applicant in replying to this Office action must make affirmation of this

election. Claims 12-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

All claims are drawn to the same claimed invention of (group II), 12-15, have been withdrawn from consideration.

Objections

Abstract

The abstract of the inventions is objected to because it is not disclose the contents of the instant application in such a way that one skilled in the art would be able to determine the technical features.

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

Claim Rejections - 35 USC § 102

b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-5, 7-11, 16-21, and 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Halverson et al., WO9953319, 21 October 1999. Halverson et al., teaches a method of transferring molecule and preparing molecules for transfer molecules positioned within a matrix to a laminate comprising:

i) a substrate comprising a shrinkable polymeric film. Here, Halverson et al., states, "an elastomeric substrate is stretched and functionalized to create linking agents on the surface of the substrate"(Pg. 4, ll, 16-18). Halverson et al., further states "The surface area of the substrate surface may be reduced, thereby increasing the density of the linking agents on the substrate"(Pg. 4, ll, 13-14). Halverson et al., further states "the arrays of the of the present invention facilitate the affixation of a high concentration of reactant at each binding site, with all the attendant advantages of high density, including the ability to increase detection signal strength. And "an elastomeric substrate is stretched and functionalized to create linking agents on the surface of the substrate"(Pg. 4, ll, 16-18).

ii) a hydrogel disposed on the substrate, to transfer one or ,more molecules from the matrix to the laminate. Here, Halverson et al., states, "In one embodiment of the present invention, array includes a polymeric substrate and a coating comprising linking agents at least partially adhered thereto. (Pg. 3, ll, 7-8) and "the high topological surface area arrays are particular useful in this regard. In addition, these high surface area arrays allow sample containing analyte(s) of interest to rapidly come in to contact with reactants, without the necessity of diffusing into a **thick** coating, such as a hydrogel (Pg. 3, ll, 25-31) and "a heat shrinkable film is functionalized to create linking agents on the surface of the film for subsequent attachment of reactants" (Pg. 4, ll, 11-13).

2. In regards to claim 2, Halverson et al., also states, "that a wide variety of coatings may be suitable for the present invention which encompasses the limitation of the generic term "hydrogel" such as an polyacrylamide gel, (Pg. 12, ll, 23-30, and Example 11).

3. In regard to claim 3, Halverson et al., discloses, "the preferable linking agents are azlactone moieties such as those provided by copolymers as taught in US Patent Nos. 4,304,705; 4,451,619; 5,262,484; 5,344,701; and 5,403,902" (Pg. 12, ll, 21-24).

4. In regard to claims 4, and 5, Halverson et al., teaches, "alternatively, more than one polymeric layer compromising linking agents may be overcoated by a second coating comprising another linking agent coating comprising linking agents" (Pg. 13, ll, 30-33).

5. In regard to claim 8, Here, Halverson et al., teaches that the matrix may contain, and with limitation, amino acids, nucleic acids, including oligonucleotides and cDNA, carbohydrates, and proteins such as enzymes and antibodies (Pg. 7, ll, 12-15).

6. In regard to claims 9-11, Halverson et al., teaches the detection and comparison of molecules transferred to a heat shrinkable film laminate (see Example 17, Pg. 33-35). Halverson et al., discloses that oligonucleotides were hybridized after two hours of incubation and that the samples were detected by fluorescent intensity (Pg. 34, ll, 15-35).

7. In regards to claim 16, Halverson et al., teaches, a polymeric substrate which includes a major surface having a major surface area and shrinking the polymeric substrate so that the topographical surface area is greater than the projected surface area and as a result a reactant such as DNA which affixed to the major surface of the substrate creating binding sites of the surface area of the majority surface is reduced, thereby increasing the density of the binding sites on the substrate, (Pg. 3-4, ll, 30-35 and 1-10 and 24-26).

8. In regards to claims 17, as stated above, Halverson et al., teaches method of preparing transferring molecules positioned within a matrix to a laminate comprising:

i) a substrate comprising a shrinkable polymeric film, and Here, Halverson et al., states "an elastomeric substrate is stretched and functionalized to create linking agents on the surface of the substrate"(Pg. 4, ll, 16-18). Halverson et al., further states "The surface area of the substrate surface may be reduced, thereby increasing the density of the linking agents on the substrate"(Pg. 4, ll, 13-

14). Halverson et al., further states "the arrays of the of the present invention facilitate the affixation of a high concentration of reactant at each binding site, with all the attendant advantages of high density, including the ability to increase detection signal strength. And "an elastomeric substrate is stretched and functionalized to create linking agents on the surface of the substrate"(Pg. 4, ll, 16-18, also see Examples 1-6, pp. 20-25)

ii) a hydrogel disposed on the substrate, to transfer one or ,more molecules from the matrix to the laminate. Here, Halverson et al., states, "In one embodiment of the present invention, array includes a polymeric substrate and a coating comprising linking agents at least partially adhered thereto. (Pg. 3, ll, 7-8) and "the high topological surface area arrays are particular useful in this regard. In addition, these high surface area arrays allow sample containing analyte(s) of interest to rapidly come in to contact with reactants, without the necessity of diffusing into a **thick** coating, such as a hydrogel (Pg. 3, ll 25-31) and "a heat shrinkable film is functionalized to create linking agents on the surface of the film for subsequent attachment of reactants" (Pg. 4, ll, 11-13), especially Examples 6, 11-17). Halverson et al., also states, "that a wide variety of coatings may be suitable for the present invention which encompasses the limitation of the generic term "hydrogel" such as an polyacrylamide gel, (Pg. 12, ll, 23-30, and especially see Example 11 and 15).

9. In regard to claims 18, 19, and 20, Halverson et al., teaches, "alternatively, more than one polymeric layer compromising linking agents may be overcoated by a second

coating comprising another linking agent coating comprising linking agents" (Pg. 13, ll, 30-33).

10. In regard to claim 21, Halverson et al., discloses, "the preferable linking agents are azlactone moieties such as those provided by copolymers as taught in US Patent Nos. 4,304,705; 4,451,619; 5,262,484; 5,344,701; and 5,403,902" (Pg. 12, ll, 21-24).

11. In regard to claim 23, Here, Halverson et al., teaches that the matrix may contain, and with limitation, amino acids, nucleic acids, including oligonucleotides and cDNA, carbohydrates, and proteins such as enzymes and antibodies (Pg. 7, ll, 12-15).

12. In regards to claim 24, Halverson et al., also states, "that a wide variety of coatings may be suitable for the present invention which encompasses the limitation of the generic term "hydrogel" such as an agarose or polyacrylamide gel, (Pg. 12, ll, 23-30, and especially see Example 11 and 15).

13. In regard to claims 25, Halverson et al., teaches the detection and comparison of molecules transferred to a heat shrinkable film laminate (see Example 17, Pg. 33-35). Halverson et al., discloses that oligonucleotides were hybridized after two hours of incubation and that the samples were detected by fluorescent intensity (Pg. 34, ll, 15-35).

Claim Rejections - 35 USC § 103

103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 6 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Halverson et al., WO9953319, 21 October 1999 as applied to claims 1-5, 7-11, 16-21,

and, 23-25 above, and further in view of Kresher, US Patent No. 4,589,965, 20th May 1986.

Halverson et al., teaches that in Examples 4 and 5, passive blotting and capillary blotting used to transfer the molecule to the laminate.

Halverson et al., does not teach the application of electro-blotting techniques to the molecule transfers from the matrix to the laminate in this instant application.

Kresher, in contrast does teach the use of electro-blotting techniques for molecule transfer in a gelatin matrix.

It would be *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the method Kresher with the transfer of molecule to film laminates of Halverson since Kresher states "that a rapid and effective method for electro-blotting is provided whereby an electrophoretically resolved material in a gelatin sheet is quickly and effectively transferred to a membrane with high pattern definition and resolution" (Abstract). Kresher further states, "Electro-blotting offers significant advantages over capillary blotting in that the electro-blotting procedure is much quicker." (column 1, ll 31-33) and offers the significant advantages such as the molecules in a gel matrix that are relatively inaccessible transfer to the surface allowing for a substantially reduced analysis time (column 1, ll 62-64). An ordinary practitioner would have been motivated to use electro-blotting is provided to combine the gel matrix molecule transfers with electro-blotting in order to expedite the production of the coated film laminates.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine L. Maupin; whose telephone number is (703) 308-3617 and fax number is (703) 746-7641.

The examiner is normally in the office between the hours of 9:30 a.m. and 5:30 p.m., and telephone calls either in the morning or the mid-afternoon are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1234.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the U.S.P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 308-4242 or (703) 308-2724. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

May 15, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER

Christine L. Maupin
Examiner
Art Unit 1637

FORM PTO-892	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NO.	
NOTICE OF REFERENCES CITED		09/819,317	1637		3
		APPLICANT(S) Coleman et al.			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	A	4,589,965	5/1986	Kreisher	204	464	
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS
	L	99/53319	10/1999	WIPO	Halverson		
	M						
	N						
	O						
	P						
	Q						

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	R	
	S	
	T	
	U	

EXAMINER	DATE	
Christine Maupin	May 17, 2002	Form892ccs2106b

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05(a).)

APPENDIX III.

Serial No.: 09/819,317

Docket No.: 56066US002

Amendment and Response filed September 10, 2002.

PATENT
Docket No.: 56066US002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Patrick L. COLEMAN, Kurt J. HALVERSON, James I. HEMBRE, Sanjay L. PATIL, Anila PRABHU, Raj RAJAGOPAL, Jerald K. RASMUSSEN and Barbara C. SWENSON

Serial No.: 09/819,317
Filed: March 28, 2001

Group Art Unit: 1637

Examiner: C. Maupin

For: METHOD OF TRANSFERRING MOLECULES TO A FILM LAMINATE

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on:

September 10, 2002 — Date

Judy L. Hansen — Signature

Judy L. Hansen

AMENDMENT AND RESPONSE

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This Amendment and Response is submitted in reply to the Office Action mailed June 10, 2002.

The Office Action notes Applicants' provisional election, without traverse, to prosecute the invention of Group I, claims 1-11 and 16-25. Applicants hereby affirm the election to prosecute claims 1-11 and 16-25 and withdraw claims 12-15 from consideration.

AMENDMENTS

Please amend the application as follows:

IN THE SPECIFICATION

Please add the following to the end of the Abstract of the Disclosure at page 23, line 6. A version of the amended Abstract of the Disclosure including markings to show the changes made is provided on a separate sheet.

The method includes (a) providing a laminate that includes i) a shrinkable polymeric substrate and ii) a hydrogel that includes linking agents disposed on at least a portion of the substrate; (b) contacting the matrix with the laminate; (c) transferring molecules from the matrix to the laminate; (d) removing the matrix from the laminate; and (e) shrinking the laminate.

IN THE CLAIMS

Please cancel claims 2, 16-22, 24 and 25 without prejudice.

Please replace pending claims 1, 3 and 23 with amended claims 1, 3 and 23 set forth below. A version of the amended claims including markings to show the changes made is provided on a separate sheet.

1. (Amended) A method of transferring molecules positioned within a matrix to a laminate comprising:

(a) providing a laminate comprising

i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area, and

ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel comprising linking agents;

(b) contacting the matrix with the laminate;

(c) transferring molecules from the matrix to the laminate;

(d) removing the matrix from the laminate; and

(e) shrinking the laminate so that the topographical surface area is greater than the projected surface area.

3. (Amended) The method of claim 1 wherein the linking agents comprise azlactone copolymers.

23. (Amended) The method of claim 1 wherein the molecules comprise polynucleotides, polypeptides, polysaccharides, or combinations thereof.

Please add the following new claim.

26. (New) The method of claim 1 wherein the step of transferring molecules from the matrix to the laminate comprises forming covalently bonds between at least a portion of the molecules and the linking agents.

REMARKS

The Abstract of the Disclosure has been amended as requested in the Office Action. No new matter has been introduced into the application as a result of the amendment.

Claims 1-25 are pending in the application. Claims 12-15 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1 and 23 have been amended. Claims 2, 16-22, 24, and 25 have been canceled. Claim 26 has been added. Claims 1, 3-11, 23 and 26 remain under consideration.

Claims 1-5, 7-11, 16-21 and 23-25 stand rejected under 35 U.S.C. § 102(b). Claims 6 and 22 stand rejected under 35 U.S.C. § 103(a).

Claim 1 has been amended to more particularly point out and distinctly claim the subject matter that the Applicants consider to be their invention. No new matter is introduced by the amendment. Support for the amendment may be found throughout the application and, in particular, in original claims 2, 16, and 20.

Claim 23 has been amended to more particularly point out and distinctly claim the subject matter that the Applicants consider to be their invention and to change its dependency from claim 16 to claim 1. No new matter is introduced by the amendment.

Claim 26 has been added to recite the method of claim 1 wherein the step of transferring molecules from the matrix to the laminate comprises forming covalently bonds between at least a portion of the molecules and the linking

agents. No new matter is introduced by this amendment. Support for the amendment may be found throughout the application and, in particular, at page 10, lines 4 and 5.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 1-5, 7-11, 16-21 and 23-25 stand rejected under 35 U.S.C. §102(b) as being anticipated by International Publication No. WO 99/53319 ("Halverson"). Claims 2, 16-21, 24 and 25 have been canceled. Of the remaining claims, only claim 1 is independent. Applicants respectfully traverse the rejection.

The Office Action states that Halverson teaches a method of transferring molecules and preparing molecules positioned within a matrix to a laminate. Applicants disagree with the characterization of Halverson set forth in the Office Action. Halverson discloses high-density miniaturized arrays and methods of manufacturing high-density miniaturized arrays. The methods of making the arrays include affixing one or more reactants directly to the array substrate by spotting, as exemplified in Example 4 using a capillary tube and in Example 5 using an aluminum post.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP § 2131. Applicants submit that Halverson does not anticipate claim 1 as amended above because Halverson does not describe each and every element of the claim.

Claim 1 recites, in part:

> A method of transferring molecules positioned within a matrix to a laminate comprising:...
> (b) contacting the matrix with a laminate;
> (c) transferring molecules from the matrix to the laminate;
> (d) removing the matrix from the laminate;...

Specifically, Applicants' submit that Halverson fails to describe 1) contacting the matrix with a laminate, 2) transferring molecules from a matrix to a laminate, or 3) removing a matrix from a laminate.

Claim 1 recites a method of transferring molecules from within a matrix to a laminate using a blotting technique. The blotting technique includes contacting a

matrix (e.g., agarose or polyacrylamide, see p. 5, lines 15-29) with a laminate so that one or more molecules positioned within the matrix can be transferred to the laminate. The matrix is characterized as suitable for separating molecules.

In contrast, Halverson describes affixing reactant molecules by spotting reactant molecules onto the substrate to form one or more discrete binding sites. Reactant molecules are spotted onto the substrate from, for example, the end of a capillary (p. 23, lines 22-24) or an aluminum post (p. 24, lines 27-30). Contrary to the characterization of Halverson in the Office Action, Halverson does not teach or suggest the transfer of reactant molecules to a substrate from a matrix or any other medium suitable for separating molecules.

Because Halverson does not describe each and every element of the claim, Halverson cannot anticipate claim 1. Because each of claims 3-5, 7-11, and 23 depends from claim 1, Halverson does not describe each and every element of, and therefore cannot anticipate, any of claims 3-5, 7-11, and 23. Reconsideration and withdrawal of the rejections of claims 1, 3-5, 7-11, and 23 under 35 U.S.C. §102(b) is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 6 and 22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over International Publication No. WO 99/53319 ("Halverson"), as applied to claims 1-5, 7-11, 16-21 and 23-25, and further in view of U.S. Patent No. 4,589,965 ("Kreisher"). Claim 22 has been canceled.

The Office Action characterizes Kreisher as teaching the use of electroblotting techniques for transferring molecules from a gelatin matrix to a blot membrane. Therefore, the Office Action asserts, it would have been obvious for one of ordinary skill in the art to utilize the method of Kreisher to transfer molecules to the film laminates of Halverson.

Applicants respectfully traverse the rejection. Applicants submit that the combination of Halverson and Kreisher fails to establish a *prima facie* case of obviousness. Accordingly, the rejection of claim 6 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

MPEP § 706.02(j) states that, in order to establish a *prima facie* case of obviousness, three basic criteria must be met:

(1) there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference;

(2) there must be a reasonable expectation of success; and

(3) the prior art reference must teach or suggest all the claim limitations. Moreover, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and must not be based on Applicants' disclosure.

Specifically, Applicants assert that the combination of Halverson and Kreisher fail to provide motivation for combining the references as suggested in the Office Action and also fail to provide a reasonable expectation of success.

One of ordinary skill in the art at the time the invention was made would have had no motivation to combine Halverson and Kreisher as suggested in the Office Action. Kreisher teaches a method of electroblotting molecules from a gel to a blot membrane. Exemplary blot membranes include papers, nylon, nitrocellulose, DBM paper, DPT paper, and the like (column 4, lines 7-10). These are all conventional blot membranes that lack any sort of coating that includes linking agents. In contrast, Halverson teaches a substrate for an array that includes a polymeric substrate and a coating that includes linking agents at least partially adhered to the substrate (page 3, lines 7 and 8). Halverson teaches affixing reactant molecules to the substrate by spotting, such as, for example, from a capillary or an aluminum post. The coating on the substrate described in Halverson provides the substrate with unique chemical character that is distinct from conventional, uncoated blot membranes (page 10, line 10 through page 14, line 9).

In order to establish a *prima facie* case of obviousness, there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (citing *In re Dance*, 48 USPQ2d 1635,1637 (Fed. Cir. 1998)). Further, "particular findings must be made as to the reason the skilled artisan, with

no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *Id.* (quoting *In re Kotzab*, 55 USPQ2d (Fed. Cir. 2000)).

Absent Applicants' disclosure, there is no teaching or suggestion that a substrate coated in the manner of the Halverson substrate could be used in an electroblot (or, indeed, any type of blotting) transfer of molecules from a gel or any other type of matrix. Also, absent Applicants' disclosure, there is no teaching or suggestion that reactant molecules can be transferred to the substrate of Halverson by any passive or active blotting method, including electroblotting. The cited references fail to provide the requisite motivation, teaching or suggestion to make the specific combination made by Applicants. Thus, the cited references fail to establish a *prima facie* case of obviousness.

Additionally, the cited references fail to provide a reasonable expectation of success should one of ordinary skill in the art have combined the substrate of Halverson to perform the method of Kreisher. As described above, the substrate of Halverson includes a coating that includes linking agents that provides the substrate described in Halverson with unique chemical character that is distinct from conventional, uncoated blot membranes. One of skill in the art at the time the invention was made would not have known whether the coating on the Halverson substrate would have interfered with electrophoretic transfer of molecules from the gel to the substrate. Thus, until actually trying the substrate of Halverson in combination with the method of Kreisher, one of ordinary skill in the art would not have had a reasonable expectation that the molecules would transfer successfully to the substrate by electroblotting or, indeed, any blotting method. Consequently, one of skill in the art could not have had a reasonable expectation that the substrate of Halverson could be used successfully in the method of Kreisher. Again, the cited references therefore fail to establish a *prima facie* case of obviousness.

In light of the arguments set forth above, Applicants submit that the combination of Halverson and Kreisher failed to establish a *prima facie* case of obviousness with regard to claim 6. Withdrawal of the rejection is kindly requested.

In light of the amendments and remarks set forth above, Applicants respectfully submit that independent claim 1 is in condition for allowance. Claims 3-11, and 23 all depend from claim 1 and are allowable for at least the reasons set forth regarding the allowability of claim 1. Accordingly, Applicants submit that each of claims 1, 3-11, and 23 are in condition for allowance for at least the reasons stated above.

NEW CLAIM

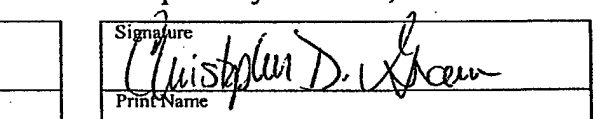
Claim 26 has been added. Claim 26 depends from claim 1 and recites that the method of transferring molecules from a matrix to a laminate includes the formation of covalent bonds between the transferred molecules and linking agents in the hydrogel coating of the laminate. Because claim 26 depends from claim 1, Applicants assert that claim 26 is allowable for at least all of the reasons set forth above regarding the allowability of claim 1.

CONCLUSION

In view of the amendments and remarks provided above, Applicants submit that all claims under consideration are in condition for allowance. Reconsideration and allowance of the claims is respectfully requested.

Respectfully submitted,

Registration Number	Telephone Number
43,643	651/733-1507
Date	
September 10, 2002	

Signature

Print Name
Christopher D. Gram

3M Office of Intellectual Property Counsel
3M Innovative Properties Company
P.O. Box 33427
St. Paul, Minnesota 55133-3427
Facsimile: 651/736-3833

VERSION WITH MARKINGS TO SHOW CHANGES MADE

A method for transferring molecules from a matrix to a laminate that includes a shrinkable polymeric film and a surface coating is disclosed. The method includes (a) providing a laminate that includes i) a shrinkable polymeric substrate and ii) a hydrogel that includes linking agents disposed on at least a portion of the substrate; (b) contacting the matrix with the laminate; (c) transferring molecules from the matrix to the laminate; (d) removing the matrix from the laminate; and (e) shrinking the laminate.

1. (Amended) A method of transferring molecules positioned within a matrix to a laminate comprising:

[contacting the matrix with] (a) providing a laminate comprising

i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area [comprising a shrinkable polymeric film], and

ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel comprising linking agents;

(b) contacting the matrix with the laminate;

(c) transferring [to transfer one or more] molecules from the matrix to the laminate;

(d) removing the matrix from the laminate; and

(e) shrinking the laminate so that the topographical surface area is greater than the projected surface area.

3. (Amended) The method of claim [2] 1 wherein the linking agents comprise azlactone copolymers.

23. (Amended) The method of claim 1[6] wherein the [matrix contains] molecules comprise polynucleotides, polypeptides, polysaccharides, or combinations thereof.

APPENDIX IV.

Serial No.: 09/819,317

Docket No.: 56066US002

Final Office Action mailed from the U.S. Patent and Trademark Office on October 30, 2002.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,317	03/28/2001	Patrick L. Coleman	56066~~USA1A.002~~ US002	4377

7590 10/30/2002

Attention: Christopher D. Gram
Office of Intellectual Property Counsel
3M Innovative Properties Company
P.O. Box 33427
St. Paul, MN 55133-3427

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 10/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,317	COLEMAN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15,23 and 26* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3-11, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Halverson et al (WO 99/53319) in view of Kreisher et al (U.S. Patent 4,589,965).

Halverson teaches a method of transferring molecules to a laminate (see page 6, lines 12-17) comprising:

(a) providing a laminate (see page 3) comprising

i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area (see page 3, lines 7-16)

ii) a hydrogel disposed on at least a portion of the substrate (see page 8, lines 9-18, page 9, lines 8-35 and page 10, lines 5-9),

(b) contacting the laminate with the molecules to be affixed (see page 6, lines 12-17 and page 17, lines 19-35)

(c) transferring said molecules to the laminate (see page 17, lines 19-35)

(d) removing the laminate from the transfer process (see page 17, lines 19-35)

(e) shrinking the laminate so that the topographical surface area is greater than the projected surface area (see page 3, lines 7-31, page 11, lines 16-22, page 37, claims 8-10).

Halverson teaches the use of azlactone copolymers (see page 12, line 33-35). Halverson further teaches the use of a masking layer (see page 13, lines 30-33) as well as coating nucleic acids, amino acids and proteins onto the laminate (see page 7, lines 12-15). Halverson further teaches detection of the molecules transferred onto the laminate (see example 17, pages 33-35). Halverson further teaches the use of covalently bonded linkage moieties (see page 6, line 13).

Halverson does not teach transfer of the molecules using a matrix to the laminate.

Kreisher et al (U.S. Patent 4,589,965) teaches electroblot transfer of molecules from a matrix to an immobilizing material (see column 2, lines 3-67). In particular, Kreisher teaches the steps of

(b) contacting the matrix with the immobilizing material (see column 2, lines 35-43)

(c) transferring the molecules from the matix to the immobilizing material (see column 2, lines 55-60)

(d) removing the matrix from the immobilizing material (column 5, lines 61-62).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to transfer the molecules onto the laminates of Halverson using the electroblot method of Kreisher since Halverson expressly states "'Affix' shall

include any mode of attaching reactants to a substrate. Such modes shall include, without limitation, covalent and ionic binding, adherence, such as with an adhesive, and physical entrapment within a substrate (page 6, lines 12-14)". An ordinary practitioner, faced with the express suggestion of Halverson to "affix" the molecules by any desirable method, would have been motivated to select the method of Kreisher since Kreisher states "Therefore it is a principal advantage of the present invention to provide a rapid and efficient method for electroblotting (cee column 2, lines 19-21)." Kreisher continues a sentence later to note "It is an additional object of the present invention to provide a method as aforesaid which obtains high resolution and absence of diffusion (see column 2, lines 25-27)." An ordinary practitioner would have been motivated to follow the express suggestion of Halverson to affix the molecules using multiple modes and to utilize the mode of Kreisher since Kreisher indicates that the electroblotting method is fast, it is efficient and it has high resolution, all characteristics desirable to Halverson, in particular the high resolution.

Response to Arguments

3. Applicant's arguments filed September 16, 2002 have been fully considered but they are not persuasive.

The 102 rejection is withdrawn in view of the amendment, and the arguments are consequently moot with regard to this rejection.

The 103 rejection is modified to directly address the amended claims, but is maintained.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection. However, the best motivation is provided in the Halvorsen reference, which suggests that any mode of affixing the molecules is desired.

4. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant then argues this is an obvious to try situation with no reasonable expectation of success. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell ,

853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art of Kreisher that molecules can be transferred by electrophoretic means from one support to another support. This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art of Kreisher directly points to the use of electroblotting as a means of transferring molecules from one support to another. This is also not a situation where

only general guidance was given. The prior art provides specific guidance directing the use of electroblotting and Halversen expressly suggests that any known means of affixing is desirable (see column 6) and Kreisher provides a known means of affixing as discussed in the rejection. Applicant's argument that a coating might have interfered with the transfer does not overcome Halverson's teaching of an expectation of success since Halveron expressly indicates that any mode of affixing would be expected to function (see column 6).

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

October 29, 2002

APPENDIX V.

Serial No.: 09/819,317

Docket No.: 56066US002

Amendment and Response Under 37 C.F.R. §1.116 filed January 29, 2003.

OFFICIAL
Expedited Examining Procedure
Group 1637

PATENT
Docket No. 56066US002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Patrick L. COLEMAN et al.	Group Art Unit:	1637
Serial No.:	09/819,317	Examiner:	J. N. Fredman
Confirmation No.:	4377		
Filed:	28 March 2001		

For: METHOD OF TRANSFERRING MOLECULES TO A FILM LAMINATE

AMENDMENT AND RESPONSE UNDER 37 CFR §1.116

Assistant Commissioner for Patents
Attn: BOX AF
Washington D.C. 20231

Dear Sir:

In response to the Final Office Action mailed 30 October 2002, please amend the above-identified application as follows:

In the Claims

Please cancel claims 12-15. Please amend claim 26. The amended claim is provided below in clean form. Per 37 C.F.R. §1.121, the amended claim is also shown in Appendix A with notations to indicate changes made (for convenience, all pending claims, including those added hereby, are provided in Appendix A).

26. **(Amended)** The method of claim 1 wherein the step of transferring molecules from the matrix to the laminate comprises forming covalent bonds between at least a portion of the molecules and the linking agents.

Remarks

The Final Office Action mailed October 30, 2002 has been received and reviewed. Claims 12-15 having been canceled, and claim 26 having been amended, the pending claims are claims 1, 3-11, 23 and 26.

Claim 26 has been amended to correct an obvious typographical error.

Reconsideration and withdrawal of the rejections are respectfully requested.

Applicants' Invention

Applicants' presently disclosed invention relates to a method of transferring molecules positioned within a matrix to a laminate. Notably, the specification (e.g., page 5, lines 15-25) describes a matrix as follows:

> The matrix of the claimed method can be any matrix suitable for separating molecules. Such separation can be based on differences in the size, shape, electrical charge or any other physical or chemical property of the molecules that can be the basis for separating molecules from one another in a mixture. As nonlimiting examples, agarose gels are known to be useful for separating polynucleotides and polyacrylamide gradient gels containing sodium dodecyl sulfate (SDS) are known to be useful for separating polypeptides, e.g., proteins. The matrix may be of uniform concentration throughout, such as a 1% agarose, which may be used to separate polynucleotides. Alternatively, the matrix may be a gradient, such as a 4-15% SDS-polyacrylamide gel for the separation of proteins. Other possible types of gels are known and may be used for the claimed method. One of skill in the art will be able to select a matrix appropriate for any desired application.

The method includes: (a) providing a laminate including i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area, and ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel including linking agents; (b) contacting the matrix with the laminate; (c) transferring molecules from the matrix to the

laminate; (d) removing the matrix from the laminate; and (e) shrinking the laminate so that the topographical surface area is greater than the projected surface area.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 1, 3-11, 23, and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over PCT International Publication No. WO 99/53319 (Halverson et al.) in view of U.S. Pat. No. 4,589,965 (Kreisher et al.). Applicants respectfully traverse the rejection.

"To establish a *prima facie* case of obviousness . . . [f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success." M.P.E.P. §706.02(j). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Halverson et al. disclose high-density miniaturized arrays and methods of manufacturing high-density miniaturized arrays. The methods of making the arrays include affixing one or more reactants directly to the array substrate by spotting, as exemplified in Example 4 using a capillary tube and in Example 5 using an aluminum post. As acknowledged by the Examiner, Halverson et al. lack specific disclosures of transferring *molecules positioned within a matrix*, contacting *the matrix with the laminate*, transferring molecules *from the matrix to the laminate*, and removing *the matrix from the laminate*.

Kreisher et al. disclose a method of electroblotting molecules from a gel to a blot membrane:

> The electrophoretically resolved material in the gelatin sheet is placed in contacting relationship with an immobilizing material. *Any suitable immobilizing material* can be used, such as membranes, papers, nylon, nitrocellulose, diazobenzyloxymethyl (DBM) paper, diazophenylthioether (DPT) paper, and the like.

(Column 4, lines 5-10, emphasis added). However, Kreisher et al. lack, among other things, a disclosure of (1) a laminate including i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area, and ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel including linking agents, and (2) shrinking the laminate so that the topographical surface area is greater than the projected surface area.

"The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. §706.02(j). Applicants respectfully submit that, absent Applicants' present disclosure, it would *not be obvious* to one of skill in the art that the laminate disclosed by Halverson et al. would be a *suitable immobilizing material* for use in the method of electroblotting disclosed by Kreisher et al.

Membranes and Papers are Suitable Immobilizing Materials for Use in Electroblotting Methods.

Electrophoretic transfer or electroblotting is defined as "a development of the technique of blot transfer, in which proteins or nucleic acids are transferred from a separation gel to nitrocellulose or diethylaminoethyl- (DEAE-)cellulose *membranes* or to diazobenzyloxymethyl- (DBM)- or diazophenylthioether- (DPT-) *paper* by electrophoresis" (EXHIBIT A: Oxford Dictionary of Biochemistry and Molecular Biology, Oxford University Press, 1997, emphasis added).

Consistent with the standard description of an immobilizing material, Kreisher et al. describe *suitable immobilizing materials* as "*membranes, papers*, nylon, nitrocellulose, diazobenzyloxymethyl (DBM) *paper*, diazophenylthioether (DPT) *paper*, and the like" (column 4, lines 7-10, emphasis added).

Halverson et al. Fail to Specifically Disclose an Array that is a Membrane or Paper.

Halverson et al. disclose arrays as including a "substrate with a coating of linking

agents" (Abstract). Halverson et al. state that "[t]he substrate of the present invention is a polymeric material" (page 7, line 32). Halverson et al. further state that "[t]he substrate provides a preferably non-porous surface upon which coatings and/or reactants may be affixed" (page 8, lines 34-35). Halverson et al. describe in detail materials that are useful for substrates including polymeric materials (e.g., page 8, lines 9-18), preferred oriented films (e.g., page 8, line 19 to page 9, line 35), and elastomeric materials (e.g., page 10, lines 5-9). However, Halverson et al. fail to specifically disclose an array that is a membrane or paper.

One of Skill in the Art Would Have No Reasonable Expectation of Success in Using an Array of Halverson et al. as an Immobilizing Material in the Electroblotting Method of Kreisher et al.

One of skill in the art might arguably have a reasonable expectation of success in using a *porous* material (e.g., a membrane or paper) as an immobilizing material in the electroblotting method of Kreisher et al. However, Halverson et al. not only fail to specifically disclose an array that is a porous material, they in fact *teach away* from an array that is a porous material by suggesting that the array includes a substrate that provides a preferably *non-porous* surface (e.g., page 8, lines 34-35).

Thus, absent Applicants' present disclosure, one of skill in the art would have no motivation to use an array as disclosed by Halverson et al. as an immobilizing material in the electroblotting method of Kreisher et al., with a reasonable expectation of success.

In light of the remarks presented herein above, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103.

Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Patrick L. COLEMAN et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228

January 29, 2003
Date

By: _____
Loren D. Albin
Reg. No. 37,763
Direct Dial (612)305-1225

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Attn: BOX AF, Washington, D.C. 20231, on this 29 day of January, 2003, at 3:38 p.m. (Central Time).

By: _____
Name: Rachel Gylland-Graham

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/819,317
Docket No.: 56066US002

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been marked in bold typeface.

In the Claims

For convenience, all pending claims are shown below.

1. A method of transferring molecules positioned within a matrix to a laminate comprising:

(a) providing a laminate comprising

i) a shrinkable polymeric substrate having a projected surface area and a topographical surface area, and

ii) a hydrogel disposed on at least a portion of the substrate, the hydrogel comprising linking agents;

(b) contacting the matrix with the laminate;

(c) transferring molecules from the matrix to the laminate;

(d) removing the matrix from the laminate; and

(e) shrinking the laminate so that the topographical surface area is greater than the projected surface area.

3. The method of claim 1 wherein the linking agents comprise azlactone copolymers.

4. The method of claim 1 wherein the laminate further comprises a mask layer.

5. The method of claim 4 wherein the mask layer is in direct contact with the substrate and underlies the hydrogel.

6. The method of claim 1 wherein the one or more molecules are transferred from the matrix to the laminate by electroblotting.

7. The method of claim 1 wherein the matrix contains polynucleotides, polypeptides, polysaccharides, or combinations thereof.

8. The method of claim 1 wherein the matrix comprises an agarose gel or a polyacrylamide gel.

9. The method of claim 1 further comprising detecting the one or more molecules transferred from the matrix to the laminate.

10. The method of claim 1 wherein the shrinkable polymeric film is flexible.

11. The method of claim 1 wherein the shrinkable polymeric film is heat-shrinkable.

23. The method of claim 1 wherein the molecules comprise polynucleotides, polypeptides, polysaccharides, or combinations thereof.

26. **(Amended)** The method of claim 1 wherein the step of transferring molecules from the matrix to the laminate comprises forming **[covalently]**<u>**covalent**</u> bonds between at least a portion of the molecules and the linking agents.

Exhibit A

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electronvolt *or* **electron volt** *symbol*: eV; a non-SI unit of energy equal to the kinetic energy acquired by an electron when accelerated through an electric potential difference of 1 volt. 1 eV = $e \times V \approx 1.602\ 18 \times 10^{-19}$ J, where e is the **elementary charge** and V is the volt.

electroosmosis *or (formerly)* **electroendosmosis** the motion of a liquid through a membrane (or plug or capillary) consequent upon the application of an electric field across the membrane. A similar phenomenon may occur in electrophoresis, where many of the supporting media used, e.g. paper or agar, acquire negative charges during electrophoresis at alkaline pHs and, since the medium cannot move, H_3O^+ ions move towards the cathode, giving the effect of an osmotic movement of solvent towards the cathode and making electrically neutral molecules appear to be cationic. —**electroosmotic** *adj.*

electropherogram *a variant spelling of* **electrophoretogram.**

electrophile *or* **electrophilic reagent** any chemical species that is preferentially attracted to a region of high electron density in another species during a chemical reaction. Such reagents normally are positively charged or contain electron-deficient chemical groups. They tend to react with electron-rich or negatively charged chemical species. *Compare* **nucleophile.**

electrophilic 1 of, pertaining to, or being an **electrophile**; having or involving an affinity for regions of high electron density in a chemical reactant. 2 describing a chemical reaction in which an electrophile participates.

electrophilic catalysis catalysis by a Lewis acid, i.e. any chemical species that abstracts an electron pair from the reactant.

electrophilic displacement *an alternative term for* **electrophilic substitution reaction.**

electrophilicity the relative reactivity of an **electrophile**, measured by the relative rate constants of different electrophiles towards a common reactant.

electrophilic reagent *an alternative name for* **electrophile.**

electrophilic substitution reaction *or* **electrophilic displacement** a chemical reaction in which an **electrophile** effects heterolytic substitution in another reactant, both bonding electrons being supplied by that other reactant.

electrophoresis 1 the phenomenon of the movement of ions (including macromolecular ions) or charged particles or ions through a fluid under the influence of an electric field applied to the fluid. A number of different media have been used as the fluid support, including paper, cellulose acetate, starch gel, and polycrylamide gel. Ions or particles bearing a net positive charge tend to move towards the negative pole of the electric field and vice versa, the rate of movement of a particular variety of ion or particle depending, *inter alia*, on its charge-to-mass ratio. The phenomenon has been widely applied in separating proteins, nucleic acids, and other charged molecular species for analytical or preparative purposes, and also in the analytical or preparative fractionation of heterogeneous populations of dispersed cells or other types of macroscopic particles. 2 the act or process of causing ions or charged particles so to migrate; any technique based upon such a phenomenon, e.g. **continuous flow electrophoresis, immunoelectrophoresis, moving boundary electrophoresis, paper electrophoresis, polycrylamide gel electrophoresis, zone electrophoresis.** *See also* **electrodecantation.** —**electrophoretic** *adj.*

electrophoresis convection *an alternative term for* **electrodecantation.**

electrophoretic effect the phenomenon of decreased **electrophoretic mobility** of a charged macromolecule caused by the movement of counter ions and/or solvent molecules in the opposite direction to that of the macromolecule.

electrophoretic mobility *symbol*: u; the **electrophoretic velocity**, v, of a charged particle expressed per unit field strength; hence, $u = v/E$, where E is the field strength. The value of u is positive if the particle moves towards the pole of lower potential and negative in the opposite case. The electrophoretic mobility depends only on molecular parameters.

electrophoretic molecular sieving *(sometimes) an alternative term for* **polyacrylamide (gel) electrophoresis.**

electrophoretic titration curve the pH-mobility curve of an ampholyte, e.g. a protein, generated by subjecting a zone of it to electrophoresis in a gel slab at right angles to a preformed, stationary pH gradient. *Compare* **isoelectric focusing.**

electrophoretic transfer *or* **electroblotting** a development of the technique of blot transfer, in which proteins or nucleic acids are transferred from a separation gel to nitrocellulose or diethylaminoethyl- (DEAE-)cellulose membranes or to diazobenzyloxymethyl- (DBM)- or diazophenylthioether- (DPT-) paper by electrophoresis, rather than by capillary flow, with a consequent decrease in the time required for the transfer. The membrane or paper bearing a resultant pattern of separated substances has been termed an **electroblot.** *See* **blotting.**

electrophoretic velocity *symbol*: v; the velocity of a charged particle during electrophoresis. It is normally proportional to the electric field strength. *Compare* **electrophoretic mobility.**

electrophoretogram *or* **electropherogram** the result of a zone-electrophoretic separation, either directly visible or after staining or processing to produce a graph.

electrophysiology the part of physiology concerned with the electrical phenomena associated with bodily processes, such as nervous and muscular activity.

electroporate to create momentary pores in the membranes of living cells, without loss of their viability, by exposing them to a sequence of brief electrical pulses of high field strength. The reversible breakdown of the cell membranes thus caused enables treated cells to take up exogenous material (e.g. drugs or foreign DNA). —**electroporated** *adj.*; **electroporation** *n.*

electroporator an apparatus or device for effecting electroporation.

electropositive 1 describing an atom or group of atoms that tends to give up electrons, especially in the formation of a covalent bond. 2 describing any chemical or other entity that carries a positive charge and hence tends to move to the cathode in **electrophoresis.**

electropositivity a measure of the power of an atom or group of atoms to give up electrons to other parts of the same molecular entity.

electrospray a technique used in **mass spectrometry** in which a dilute acidic solution of the macromolecule is sprayed from a metal syringe needle maintained at +5000 V, forming fine highly charged droplets from which the solvent rapidly evaporates.

electrostatic of or pertaining to static electricity or electrostatics.

electrostatic bond any valency linkage between atoms arising from the transfer of one or more outer-shell electrons of one atom to the outer shell of another atom, leading to more complete outer shells in both atoms. The dissociation of an electrostatic bond leads to the production of ions.

electrostatic field any **electric field** produced by stationary charges.

electrostatic interaction any of the attractive or repulsive forces between atoms and/or groups of atoms and/or molecules that are due to the presence of ionized chemical entities and to the electronegative and electropositive properties of these atoms, groups, or molecules. *Compare* **electric field.**

electrostatic precipitation the removal of small particles suspended in a gas by electrostatic charging followed by precipitation onto a highly charged collector.

electrostatics the branch of physics concerned with static electricity.

electrostatic units *abbr*: esu *or* ESU; a system of electrical units, used in the cgs system, based upon the electrostatic unit of electric charge, i.e. the quantity of electricity that will repel an equal quantity of electricity, 1 cm distant from it in a vacuum, with the force of 1 dyne.

electrostriction the reversible change in dimensions of a dielectric when an electric field is applied to it. For example, the

APPENDIX VI.

Serial No.: 09/819,317

Docket No.: 56066US002

Advisory Action sent by facsimile from the U.S. Patent and Trademark Office on February 5, 2003.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,317	03/28/2001	Patrick L. Coleman	56066~~USA1A.002~~ US002	4377

32692 7590 02/05/2003

3M INNOVATIVE PROPERTIES COMPANY
PO BOX 33427
ST. PAUL, MN 55133-3427

EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1637	8

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/819,317	COLEMAN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 January 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1,3-11,23 and 26*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *6*.

10. ☐ Other: _____

Jeffrey Fredman
Primary Examiner
Art Unit: 1637

Continuation of 5. does NOT place the application in condition for allowance because: Applicant argues that that Halverson lacks a disclosure of transferring molecules positioned within a matrix, contacting the matrix with a laminate, transferring molecules from the matrix and removing the matrix from the laminate. This argument is not correct. As noted in the rejection, Halverson expressly teaches contacting the laminate with the molecules to be affixed. For example, Halverson states "Reactants, such as DNA, may be affixed to the substrate via linking agents (see page 4, lines 18-19)". Halverson than teaches the actual affixation, which is a transferral of the molecules onto the laminate at page 17 as previously discussed, as well as the steps of transferring and removal, which represents completion of the transfer. Applicant then argues that there is no motivation to combine the references. As noted previously, Halverson specifically notes that a variety of modes of attachment are available and Kreisher teaches a desirable means of attaching the components. Applicant then performs a piecemeal analysis of each reference. It is the combination that renders the claim obvious, not either reference alone. The argument regarding reasonable expectation of success was previously addressed..

INFORMATION DISCLOSURE STATEMENT

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Applicant(s): Patrick L. Coleman, Kurt J. Halverson, James I. Hembre, Sanjay L. Patil, Anila Prabhu, Raj Rajagopal, Jerald K. Rasmussen and Barbara W. Swenson	
Filing Date: March 28, 2001	Group: 1637

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	SubClass	Filing Date If Appropriate
✓		3,498,788	03/03/70	Haas	96	76	
✓		4,322,461	03/30/82	Raphael et al.	428	14	
✓		6,207,077 B1	03/27/01	Burnell-Jones	252	301	

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	SubClass	Translation Yes	Translation No
✓		0 388 532 A1	09/26/90	EPO	G03C	8/56	X	
✓		0 608 872 A1	08/03/94	EPO	G01N	27/406	X	
✓		01231897	09/18/89	Patent Abstract of Japan	C12Q	1/54	X	
✓		05274640	10/22/93	Patent Abstract of Japan	G11B	5/627	X	
✓		WO 00/10007	02/24/00	PCT	G01N	33/487	X	

OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)

EXAMINER	Date Considered
✓	2/03/03

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Based on Form PTO-FB-A820
(Also form PTO-1449)

Patent and Trademark Office, U.S. Department of Commerce

APPENDIX VII.

Serial No.: 09/819,317

Docket No.: 56066US002

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1. Halverson et al. (PCTInternational Publication No. WO 99/53319).
2. Kreisher et al. (U.S. Patent No. 4,589,965).

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(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133–3427 (US).

(72) Inventors: HALVERSON, Kurt, J.; P.O. Box 33427, Saint Paul, MN 55133–3427 (US). PATIL, Sanjay, L.; P.O. Box 33427, Saint Paul, MN 55133–3427 (US). RASMUSSEN, Jerald, K.; Post Office Box 33427, Saint Paul, MN 55133–3427 (US).

(74) Agents: ROGERS, James, A. et al.; Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133–3427 (US).

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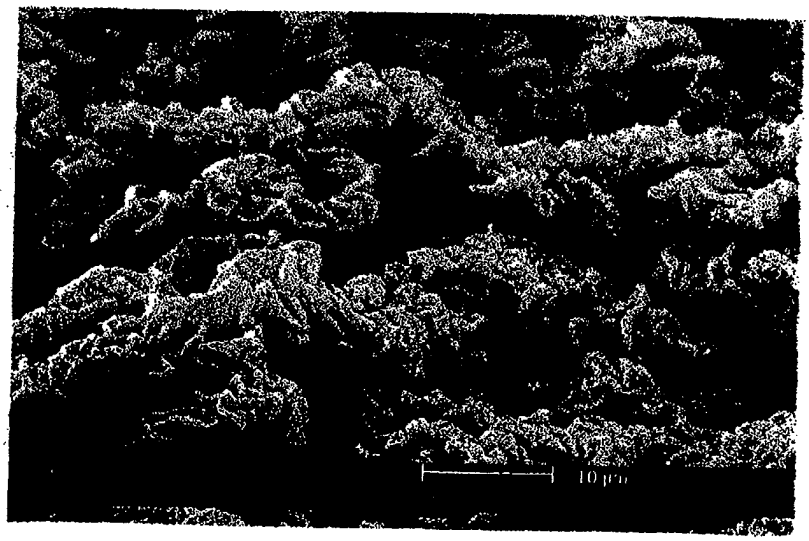
(54) Title: HIGH–DENSITY, MINIATURIZED ARRAYS AND METHODS OF MANUFACTURING SAME

(57) Abstract

High–density, miniaturized arrays including high surface areas. Arrays described include substrate with a coating of linking agents, as well as arrays with reactants affixed to the substrates. Methods of manufacturing high–density arrays of reactants. The methods include the use of oriented, heat shrink films and elastomeric materials. Methods of functionalizing a substrate with linking agents for subsequent affixation of reactants are also disclosed herein.



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HIGH DENSITY, MINIATURIZED ARRAYS AND METHODS OF MANUFACTURING SAME

This invention was made with government support under Project Number 95-08-0006 awarded by the National Institute of Standards and Technology. The United States government has certain rights in the invention.

This invention relates to arrays manufactured on polymeric surfaces and more particularly to high-density, miniaturized arrays and methods of manufacturing the same.

Miniaturized arrays may be used in a variety of applications, such as gene sequencing, monitoring gene expression, gene mapping, bacterial identification, drug discovery, and combinatorial chemistry. Many of these applications involve expensive and oftentimes difficult to obtain samples and reagents. Accordingly, high density, miniaturized arrays are desirable because the use of such arrays may dramatically increase efficiency with respect to limited or expensive samples when compared to standard arrays, such as a 96 well plate. For example, a 96 well plate may require several hundred microliters of sample per well to run a diagnostic experiment whereas a miniaturized array would require only a fraction of that sample for the entire array. In addition to the reduction of volume, miniaturization allows hundreds or thousands of tests to be performed simultaneously. Furthermore, a high-density array may be more versatile than a standard array because of the wide variation of chemistries that may be present on a single array.

Current methods of manufacturing miniaturized arrays are not conducive to mass production. These methods are limited by multiple step procedures and by the difficulty in achieving miniaturized arrays with densely packed reactants. The manufacture of arrays is further complicated in applications requiring different chemistries at different binding sites on the arrays, such as required for manufacturing oligonucleotide arrays.

One example of a multiple step procedure for manufacturing arrays is disclosed in U.S. Patent No. 5,445,934. This patent discloses a method of on-chip synthesis. In this process, the substrate is derivatized with a chemical species containing a photocleavable protecting group. Selected sites are deprotected by irradiation through a mask. These sites are then reacted with a DNA monomer containing a photoprotective group. The process of masking, deprotecting and reacting is repeated for each monomer attached until an array of site-specific sequences is achieved. This process may be both time-consuming and resource intensive. Because of the planar nature of the surface, a limited concentration of oligonucleotides (measured by the distance between adjacent oligonucleotides within a binding site) can be synthesized at each binding site before steric crowding interferes with the hybridization reaction. As a result, the amount of detectable signal from each binding site may also be limited.

Another type of method used to manufacture arrays is off-chip synthesis. An example of off-chip synthesis is disclosed in U.S. Patent No. 5,552,270. This process uses gel pads. The gel pads are created on a substrate using robotic devices. Thereafter, minute quantities of presynthesized oligonucleotides are robotically placed on individual gel pads on the substrate. Production of chips using off-chip synthesis is generally time-consuming because each solution is deposited individually or in small groups. High densities are difficult to achieve because of the limited resolution of robotic devices and the physical size limitations of the fluid delivery devices. This type of process typically requires the use of specialized, sophisticated, and miniaturized tools. The use of gel pads facilitates the affixation of a higher concentration of oligonucleotides within each binding site, which may overcome the difficulties encountered with planar surfaces outlined above. However, the use of thick gel layers hinders hybridization kinetics due to slow target analyte diffusion into and out of the gel.

There is a need for high density, miniaturized arrays including reactive surfaces with high surface areas and high detection signal strength. Preferably, the arrays would facilitate rapid binding kinetics between affixed reactants and target analytes. There is a further need for methods of manufacturing high density,

miniaturized arrays. The methods preferably would be cost-effective and amenable to mass production.

In one embodiment of the present invention, an array includes a polymeric substrate and a coating comprising linking agents at least partially adhered thereto. The coating comprising linking agents has a projected surface area and a topographical surface area, and the topographical surface area is greater than the projected surface area. The topographical surface area is at least two times greater than the projected surface area. In a preferred embodiment, the topographical surface area is at least five times greater than the projected surface area. In a most preferred embodiment, the topographical surface area is at least fifteen times greater than the projected surface area. Preferably, the coating includes an undulated surface.

In a preferred embodiment of the present invention, the array includes a binding site density of over 1,000 binding sites per square centimeter. A density of at least 25,000 binding sites per square centimeter is preferred with a density of over 60,000 per square centimeter being most preferred.

In another embodiment of the present invention, a material for use in manufacturing an array includes an oriented, polymeric substrate including a coating comprising linking agents. This material is suitable for the subsequent affixation of reactants thereto.

The arrays of the present invention facilitate the affixation of a high concentration of reactants at each binding site, with all of the attendant advantages of high density, including the ability to increase detection signal strength. The high topographical surface area arrays are particularly useful in this regard. In addition, these high surface area arrays allow sample containing the analyte(s) of interest to rapidly come into contact with the reactants, without the necessity of diffusing into a thick coating, such as a hydrogel.

In one embodiment of the methods of the present invention, a polymeric substrate includes a major surface having a surface area. A reactant, such as DNA, is affixed to the major surface of the substrate to create binding sites. The surface

area of the major surface is reduced, thereby increasing the density of binding sites on the substrate.

In a preferred embodiment, the substrate is a biaxially oriented, heat shrink film. In a particularly preferred embodiment of the present invention, the reactants are oligonucleotides wherein the oligonucleotides vary in composition at differing binding sites on the substrate.

In another method of the present invention, a heat shrink film is functionalized to create linking agents on the surface of the film for subsequent attachment of reactants. The surface area of the substrate surface may be reduced, thereby increasing the density of linking agents on the substrate. Preferably, the heat shrink surface is functionalized with azlactone linking agents.

In yet another embodiment of the present invention, an elastomeric substrate is stretched and functionalized to create linking agents on the surface of the substrate. Reactants, such as DNA, may be affixed to the substrate via linking agents. The substrate is subsequently allowed to relax, thereby reducing the surface area of the substrate to increase the density of linking agents on the substrate. A backing or other structure may be added to retain the substrate in the reduced orientation.

In yet another embodiment of the present invention, a method of manufacturing arrays of the present invention includes providing an oriented polymeric substrate. A coating comprising linking agents is applied to a surface of the substrate. Subsequently, the substrate is relaxed such that it becomes less oriented or isotropic. During this relaxation step, the topographical surface area of the coating becomes greater than the projected surface area of the coating. Reactants may be affixed to the linking agents prior, during or subsequent to the relaxation step to create an array with binding sites. Preferably, the reactants are affixed prior to the relaxation step.

The methods of manufacture of the present invention are amenable to mass production. The methods of manufacture of the present invention may be employed to increase the efficiency of current methods of manufacture of arrays to achieve high densities of reactants. The methods of the present invention are particularly

useful in achieving high-density nucleic acid arrays wherein different nucleic acids are located at different sites on the substrate.

Figure 1a is side view of an array of the present invention prior to relaxation of the substrate thereof.

Figure 1b is a side view of the array of Figure 1a of the present invention subsequent to relaxation of the substrate thereof.

Figure 2 is a perspective view of an oligonucleotide array manufactured in accordance with the methods of the present invention wherein each letter represents a different oligonucleotide.

Figure 3 is an exploded view of a binding site of an array manufactured in accordance with the methods of the present invention.

Figure 4 illustrates an embodiment of the methods of the present invention.

Figure 5 illustrates another embodiment of the methods of the present invention.

Figure 6a is a scanning electron micrograph (SEM) of a substrate coated with a copolymer of dimethylacrylamide/vinyldimethylazlactone prior to relaxation of the substrate.

Figure 6b is an SEM of the coated substrate of Figure 6a subsequent to relaxation thereof.

Figure 7a is an SEM of a relaxed substrate coated with polyethylenimine.

Figure 7b is an SEM of a relaxed substrate coated with dimethylacrylamide/vinyldimethylazlactone copolymer over-coated with polyethylenimine.

Figure 8a is an SEM of a substrate coated with a carboxylated polyvinylchloride prior to relaxation of the substrate.

Figure 8b is an SEM of the coated substrate of Figure 8a subsequent to relaxation thereof.

Figure 9a is an SEM of a substrate with a low glass transition temperature copolymer subsequent to relaxation of the substrate.

Figure 9b is an SEM of a substrate with a higher glass transition temperature copolymer than that of Figure 9a, subsequent to relaxation of the substrate thereof.

The present invention provides high-density, miniaturized arrays and methods of manufacturing the same.

For purposes of this invention, the following definitions shall have the meanings set forth.

"Affix" shall include any mode of attaching reactants to a substrate. Such modes shall include, without limitation, covalent and ionic bonding, adherence, such as with an adhesive, and physical entrapment within a substrate. In the case of linking agents, reactants may be affixed to the substrate by linking agents that are created by functionalizing a surface, such as with an acid wash, or by linking agents that are coated on the substrate.

"Analyte" shall mean a molecule, compound, composition or complex, either naturally occurring or synthesized, to be detected or measured in or separated from a sample of interest. Analytes include, without limitation, proteins, peptides, amino acids, fatty acids, nucleic acids, carbohydrates, hormones, steroids, lipids, vitamins, bacteria, viruses, pharmaceuticals, and metabolites.

"Binding site" shall mean a discrete location on a substrate wherein reactants are affixed thereto. A single binding site may include a quantity of one or more of the same reactants affixed to the substrate.

"Density" shall mean a measure of quantity per unit projected area of substrate, such as, for example, linking agents per square centimeter or binding sites per square centimeter.

"Equivalent" shall mean substantially equal.

"Linking agent" shall mean any chemical species capable of affixing a "Reactant" to the substrate.

"Projected surface area" shall mean the surface area for a surface as is calculated with respect to the plane encompassing the "x" and "y" axes of the surface.

"Reactant" shall mean any chemical molecule, compound, composition or complex, either naturally occurring or synthesized, that is capable of binding an analyte in a sample of interest either alone or in conjunction with a molecule or compound that assists in binding the analyte to the substrate, such as, for example, a coenzyme. The reactants of the present invention are useful for chemical or biochemical measurement, detection or separation. Accordingly, the term "Reactant" specifically excludes molecules, compounds, compositions or complexes, such as ink, that do not bind analytes as described above. Examples of reactants include, without limitation, amino acids, nucleic acids, including oligonucleotides and cDNA, carbohydrates, and proteins such as enzymes and antibodies.

"Topographical surface area" shall mean the surface area of a surface as is calculated with respect to the planes encompassing the "x", "y" and "z" axes of the surface, or in other words, a measurement of the surface features of the coating.

"Undulations -or- undulated" shall mean convoluted, wave-like forms. For purposes of this invention, it is preferred that an undulated surface comprises undulations that are irregular as to pattern such as are depicted in Figures 6b, 7b, 8b and 9b. "Undulations -or- undulated" does not include structures such as reservoirs or microwells that are created by methods such as for example printing, embossing, casting, molding, laserscribing, photolithography, etching, mechanical scratching or scoring.

With reference to Figures 1a and 1b, the present invention 10 includes a substrate 12 with at least one major surface 14 having a surface area. The major surface 14 may be generally smooth or may include undulations. The substrate 12 may be any number of shapes. The shape of the substrate 12 is not limiting, so long as the substrate 12 provides a base for applying the coating 15 comprising linking agents and reactants 22 thereon, as described more fully below.

The substrate of the present invention is a polymeric material. The material of the substrate is selected with regard to the application for the resulting arrays. For example, the substrate preferably exhibits low background fluorescence in the event fluorescence is used for detection purposes and therefore will not

substantially interfere with the indicator systems used in the assays run on the arrays manufactured in accordance with the methods of the present invention. The substrate material preferably is compatible with the reagents and conditions of the assays, such as temperature and pH.

Many polymeric materials may be suitable for use in the present invention. However, in order to form the high surface area surface of the linking agent coating, as described more fully below, the materials are preferably capable of being oriented, i.e., films that shrink at least in one direction within the film plane when energy, preferably heat, is applied to the film for a specified period of time. Elastomeric materials, which are stretched at least in one direction prior to affixation of reactants, constrained in the stretched state during affixation of reactants, and then allowed to recover, thereby reducing the projected surface area of the substrate surface from the stretched state, are also suitable for use in the present invention.

With respect to oriented films, shrinkage need not be equal in any two orthogonal directions within the film plane, although a substantially uniform shrinkage is preferred. In considering shrinkage as a function of direction in the film plane, substantial uniformity of directionally-dependent shrinkage from point to point within the film is preferred; that is, the film preferably shrinks in substantially the same amount in each direction, regardless of position on the film plane. If the film employed does not exhibit substantially uniform shrink characteristics, a registration indicator may be added to the binding sites or otherwise employed to register the binding sites in the finished array.

While the starting substrate material of the present invention includes oriented films, the substrates of the arrays of the present invention are generally relaxed, i.e., generally no longer oriented or, in fact, isotropic. A backing may be applied to the substrate to maintain the substrate in a less than oriented state. The backing may optionally include a release liner to permit the backing to be removed if desired.

The substrate provides a preferably non-porous surface upon which coatings and/or reactants may be affixed. Upon relaxation of the oriented substrate

or reduction of the surface area of the major surface, the substrate provides support and integrity to the coatings and/or reactants thereon. In addition, the substrate maintains the relative spatial relationship of the binding sites.

Preferred oriented films include biaxially oriented low-density polyethylenes; biaxially oriented linear low-density polyethylenes; and biaxially oriented ultra low-density polyethylenes. Biaxially oriented films are preferred because they exhibit shrinkage in two orthogonal in-plane directions (hereafter referred to as the "x" and "y" directions). Other oriented films that may be suitable for use in the present invention include uniaxially, biaxially, or multiaxially oriented films made by any process known to the art, including but not limited to melt-orientation; the blown film, bubble, double-bubble, and tubular processes; length orientation; the process of tentering; extension over a mandrel; thermoforming; and blow molding. Polymers which may be employed in such films include, but are not limited to, polyethylenes, including high density polyethylene, low density polyethylene, linear low density polyethylene, ultra low density polyethylene, and copolymers of ethylene (including ethylene propylene copolymers and ethylene vinyl acetate copolymers); polyolefins, including isotactic polypropylene, syndiotactic polypropylene, and polymethylpentene; polyacetals; polyamides, including polyamide 6 and polyamide 66; polyesters, including polyethylene terephthalate, polybutylene terephthalate, and polyethylene naphthalate; halogenated polymers, including polyvinyl chloride, polyvinylidene chloride, polychlorotrifluoroethylene, polyvinyl fluoride, and polyvinylidene fluoride; styrene polymers, including general purpose polystyrene and syndiotactic polystyrene; cellulose esters, including cellulose acetate and cellulose propionate; polyketones, including polyetheretherketone and copolymers and terpolymers of carbon monoxide with ethylene and/or propylene; polycarbonates, including the polycarbonate of bisphenol A; phenyl-ring polymers, including polyphenylene sulfide; polysulfones; polyurethanes; polymers of acrylic and methacrylic acids and their esters; ionomers; and copolymers, blends, or layered structures of any of the above-named polymers. Oriented films of any of these polymers may be optionally cross-linked.

Examples of elastomeric materials that may be suitable for use in the present invention include natural rubber, polyisoprenes, polychloroprene, polyisobutylenes, polybutenes, nitriles, polyurethanes, silicones, random copolymers and terpolymers (such as ethylene-propylene copolymers and ethylene-propylene-diene monomer terpolymers), and block copolymers.

With continuing reference to Figures 1a and 1b, the array includes a coating 15 comprising linking agents. The linking agents are selected based on the reactants 22 to be affixed to the substrate 12 and the application for which the array 10 will be used.

In a preferred embodiment, the linking agents are coated onto the major surface 14 of the substrate 12 such that the coating 15 is at least partially adhered to the substrate 12. The coating 15 comprising linking agents has a projected surface area and a topographical surface area. The coating on the substrate generally is smooth in appearance, such as depicted in Figures 6a and 8a. Accordingly, the projected surface area and the topographical surface area are substantially equivalent.

As described more fully below, upon relaxation of the substrate 12, the topographical surface area becomes greater than the projected surface area. Surprisingly, the arrays 10 of the present invention include coatings 15 that are capable of exhibiting topographical surface areas that greatly exceed the projected surface areas. The topographical surface area of the coating 15 is at least two times greater than the projected surface area of the coating. Preferably, the topographical surface area is at least five times greater than the projected surface area. In a most preferred embodiment, the topographical surface area is at least fifteen times greater than the projected surface area.

In a preferred embodiment, upon relaxation of the substrate 12, as explained more fully below, the coating of linking agents 15 becomes undulated as depicted in Figures 1b, 6b, 7b, 8b and 9b. While the undulations in these figures are irregular with respect to any discernable pattern, it is contemplated that a regular pattern of undulations may be achievable in accordance with the methods of the present invention.

It is believed that this quite unexpected result is due to a variety of factors, including the adhesion properties of the coating with respect to the substrate as well as the thickness and glass transition temperature (T_g) of the coating. Upon relaxation of the substrate, a stress mismatch will develop at the substrate/coating interface due to the strain match. The adhesion of the coating to the substrate should be sufficient to prevent total delamination of the coating from the substrate. Because the desired array preferably includes an undulated surface, a degree of delamination may actually occur and still provide a useful array in accordance with the present invention. However, the degree of delamination should not be so great as to interfere with assays being conducted on the arrays or result in effective loss of the coating from the substrate.

Significantly, the inventors of the present invention discovered that heating to relax the substrate may actually improve adhesion to the coating. It is possible that, due to the undulations, the polymeric substrate and the polymeric coating form an interlocking structure. In addition, some entanglement of polymer chains may occur at the substrate/coating interface during the heating step. In both instances, upon cooling, the interlocking structures or polymer entanglements may serve to minimize delamination of the coating.

It is believed that thicker coatings will result in larger-dimensioned undulations because the flexural rigidity of the coating will vary approximately as the cube of its thickness. In theory, a flexurally stiffer object would be expected to bend at a larger radius than that of an object of less rigidity (all other variables being equal). In practice, the flexural rigidity will also be affected by the adhesion properties of the coating with respect to the substrate.

In the present invention, a coating of between about 0.1 micron and 10 microns is preferred, with a coating of less than about 1 micron being preferred in order to minimize diffusion difficulties that may arise when using thicker coatings. An analyte of interest may have to diffuse through the coating prior to contacting a reactant affixed thereto. If the coating of linking agents is relatively thick, e.g. greater than about 10 microns, the diffusion time required could slow the kinetics of the analyte/reactant interaction. Furthermore, if the coating is too thick, it may

delaminate from the substrate because of the high flexural rigidity of such a coating.

It is also believed that if the T_g of the coating is substantially lower than the T_g of the substrate, the coating will have sufficient time to undergo viscoelastic flow during reduction of the substrate surface upon which the coating is adhered. The resulting coating will be relatively smooth and lacking in significant undulations. In this instance, the projected surface area of the coating and the topographical surface area of the coating will be substantially equivalent. In addition, the coating will increase in thickness. On the other hand, it is surmised that coatings with a T_g fairly comparable to or higher than that of the substrate will not undergo sufficient viscoelastic flow during the relaxation of the substrate and accordingly will result in an undulated surface having a high topographical surface area.

In light of the foregoing, it is believed that a wide variety of coatings may be suitable for use in the present invention, provided the coatings are suitable for affixing reactants and are compatible with the assays and attendant conditions that are to be conducted on the particular array. Preferred linking agents are azlactone moieties such as those provided by copolymers as taught in U.S. Patent Nos. 4,304,705; 4,451,619; 5,262,484; 5,344,701; and 5,403,902. Especially preferred copolymers are those prepared using hydrophilic or water-soluble comonomers such as acrylamide and acrylamide derivatives, hydroxyethylacrylate and methacrylate, and the like. In addition to azlactone linking agents, copolymers including other linking agents may also be utilized. These include, for example, epoxy, carboxylic acid, hydroxyl, amine, N-hydroxysuccinimide, iso- and isothiocyanate, anhydride, aldehyde, and other groups which are well known in the art for the immobilization of reactants. The copolymers comprising linking agents may be prepared by either step growth or chain growth polymerization processes as are well known in the art.

Azlactone moieties are preferred because these moieties are suitable for reaction with numerous reactants, including oligonucleotides. Azlactone moieties are generally hydrolytically stable and therefore have a relatively long shelf life

when used in applications of the present invention. These moieties also generally exhibit high reactivity with a wide variety of reactants.

The coatings may be crosslinked or otherwise treated to insolubilize, modify the T_g or modify the adhesion properties of the coating. For example, copolymers that have a low T_g may be formulated with a cross-linker in order to raise the T_g of the resultant coating. The coatings can be applied to the substrate by any of several conventional means known in the art, such as extrusion coating, die coating, dip coating, air-knife coating, gravure coating, curtain coating, spray coating, use of wire wound coating rods, and the like. Coatings may be made from solution, followed by removal of solvent, or by hot melt coating of 100% solids formulations.

Adhesion of the coating to the substrate may be improved, if desired, by any of the methods known to one skilled in the art. These methods include various pre-treatments to or coatings on the major surface, such as corona or plasma treatment, or by application of primers. Suitable primers include, without limitation, polyethylenimine, polyvinylidenechloride, primers such as those described in U.S. Patent No. 5,602,202, and colloidal dispersions of inorganic metal oxides in combination with ambifunctional silanes such as described in U.S. Patent Nos. 5,204,219, 5,464,900, and 5,639,546. Other methods of increasing adhesion of copolymers to polyolefin substrates are disclosed in U.S. Patent No. 5,500,251.

The linking agents may be coated substantially over the entire area of a surface of the substrate, such as the major surface, or in spots that may be in a regular or irregular pattern on such surface. In the latter case, upon relaxation of the substrate, the topographical surface area of each spot will be greater than the projected surface area of such spot. Alternatively, more than one polymeric layer comprising linking agents may be coated on the substrate. A first coating of linking agents may be overcoated by a second coating comprising linking agents in order to obtain undulations in accordance with the methods of the present invention. In this manner, a coating that would otherwise not form undulations may be converted to an undulated coating. Preferably, the two coatings would

adhere to each other or chemically bond to each other. For example, the substrate may be coated with a polymer including azlactone moieties that in turn is overcoated with a second polymer including amine moieties. The amines and azlactones would react to bind the layers together, however, it is anticipated that free amines groups would remain to affix reactants, such as cDNA, to the substrate.

Reactants 22 are affixed to the substrate 12 to create binding sites 16 as depicted in Figures 1a, 1b and 3. As described more fully below, with respect to the methods of the present invention, any number of processes known in the art may be used to introduce the reactants to be affixed to the substrate. It is understood that the mode of affixation may vary in accordance with the reactant or reactants employed.

The type of reactant used in the present invention will vary according to the application and the analyte of interest. For example, when characterizing DNA, oligonucleotides are preferred. When conducting diagnostic tests to determine the presence of an antigen, antibodies are preferred. In other applications, enzymes may be preferred. Accordingly, suitable reactants include, without limitation, amino acids, nucleic acids, including oligonucleotides and cDNA, carbohydrates, and proteins such as enzymes and antibodies.

With reference to Figure 2, in a preferred embodiment, a variety of nucleic acids, such as oligonucleotides 18 (an oligonucleotide being denoted by a letter) are affixed to the substrate 12 at separate binding sites 16. The variety of oligonucleotides 18 on the substrate 12 permits a large number of potential binding events between reactants and target analytes in a sample.

The reactants may be affixed prior to, during or after reduction of the major surface or relaxation of the substrate. However, it is preferred to affix the reactants prior to reduction of the major surface or relaxation of the substrate in order to take advantage of the methods of the present invention wherein high reactant binding site densities may be achieved.

With reference to Figures 6b, 7b, 8b, and 9b, arrays of the present invention are capable of exhibiting high topographical surface areas. These high surface area arrays offer additional opportunities for increasing signal strength of the arrays.

The undulated surfaces permit more reactants to be affixed to a given area versus binding reactants to a relatively flat surface. Also, in the case where reactants are affixed prior to relaxation of the substrate, the spatial relationship of the reactants to one another on the surface is fixed. Upon relaxation of the substrate, the surface of the coating becomes undulated, in effect, increasing the density of reactants with respect to the projected surface area but substantially maintaining their relative separation due to the topographical surface area. This spacing allows presentation of a high density of reactants or binding sites at or near the surface of the coating while minimizing potential steric crowding. This, in turn, facilitates rapid interaction kinetics with prospective analytes.

With respect to the methods of the present invention and reference to Figures 4 and 5, the substrate 12 starting material is at least partially oriented. Oriented films exhibit an area shrinkage reduction that is dependent in part on the degree of elongation of the film during orientation thereof. In the methods of the present invention, the area shrinkage reduction is a measure of the area shrinkage of the film from its oriented, pre-shrunken dimensions to its dimensions after energy has been applied to shrink the film. For example, a 10 cm x 10 cm (100 cm^2 area) film that shrinks fifty percent (50%) in the "x" direction and fifty percent (50%) in the "y" direction after the application of sufficient heat will be reduced to 5 cm x 5 cm (25 cm^2 area), thereby exhibiting an area shrinkage reduction of seventy-five percent (75%). An area shrinkage reduction of about twenty-five percent (25%) is suitable for use in the present invention with an area shrinkage reduction of more than about seventy-five percent (75%) being most preferred because films exhibiting area shrinkage reductions of this magnitude are capable of achieving very high-density arrays, as more fully described below.

Referring to Figure 5, the substrate 12 is prepared. In the case of elastomeric materials, the substrate 12 is stretched in the "x" and/or "y" direction and retained in the stretched condition. Processes for stretching an elastomeric material may include using a tentering device or stretching the material over a frame or mandrel. In most applications, a uniform stretching of the substrate in both the "x" and "y" configuration is preferred so that reactants may be affixed or

bound to the substrate in parallel rows. However, other patterns of reactants may be desired, such as, for example, a fan shape array of reactants. Accordingly, the extent and pattern of stretching may be dependent on the desired shape of the finished array.

With reference to Figures 4 and 5, the surface of the substrate 12 need not be functionalized in order to affix reactants 22 thereto. However, depending on the mode of affixation, the substrate 12 may be further prepared by functionalizing the surface to create linking agents.

The type of functionalization will depend on the type of substrate and reactant(s). For example, in a preferred embodiment using an oriented film, such as oriented polyethylene, the linking agents are azlactone moieties. In addition to the azlactone copolymers set forth above, suitable azlactone functional compounds include those such as are disclosed in U.S. Patent Nos. 4,485,236 and 5,149,806. One method of functionalizing the surface includes acid washing the substrate followed by the addition of a bis-amino molecule to create an amine-functional surface, to which azlactone-linking agents are affixed. The resulting functionalized surface is capable of affixing oligonucleotides. Other processes for functionalizing polymers are known in the art and are suitable to the extent they can be employed to create linking agents for affixation of reactants, for example, the heterobifunctional cross-linking agents disclosed in U.S. Patent No. 5,436,147. The linking agents preferably remain substantially affixed to the substrate after reduction of the surface area of the major surface and further preferably are not substantially degraded by the reduction of the surface area. After functionalization, the substrate comprises a blank array, suitable for subsequent affixation of reactants.

One skilled in the art should also appreciate that a variety of approaches to rendering the surfaces of elastomeric materials chemically reactive are known and may be employed in the present invention to the extent their use creates linking agents on the substrate for subsequent affixation of reactants. The linking agents preferably remain substantially affixed to the substrate after reduction of the surface area of the major surface or relaxation of the substrate and further

preferably are not substantially degraded by such reduction or relaxation. One example of such an approach for treating surfaces for biomolecule attachment is described in U.S. Patent No. 5,258,041.

With reference to Figure 3, reactants 22 are introduced to the substrate and preferably to the major surface for affixation to create binding sites 16. The modes of affixation may include, without limitation, physical means, such as for example, physically entrapping the reactants 22 within the substrate. With reference to Figures 1a and 1b, in a preferred embodiment of the present invention, reactants 22 are introduced to be affixed to the substrate 12 using a coating 15 of linking agents. The linking agents may be coated on the substrate 12 using any of the methods described above. Preferably, the coating 15 is at least partially adhered to the major surface 14 of the substrate 12. The substrate 12 may also be primed or otherwise treated prior to such coating step in order to enhance adhesion of the coating 15 to the substrate. Suitable primers are set forth above.

Regardless of how the reactants are affixed, any number of processes known in the art may be used to introduce the reactants 22 to the substrate, including on-chip or off-chip synthesis. Using such techniques, the methods of the present invention can be used to increase array site density by greater than a factor of 20. For the purpose of high throughput manufacturing, however, sophisticated miniaturized tools and methods, such as those used in on-chip and off-chip synthesis, may not be desired. Accordingly, large quantities of reactants may be deposited in a short period of time because the initial substrate size is relatively large, such as a substrate having a 4 cm x 4 cm surface. The resulting binding sites formed may be relatively large, with areas, for example, of approximately 0.25 mm^2 to 1.0 mm^2 being suitable for use in the present invention. For example, the solutions containing the reactants 22 to be affixed may be simultaneously introduced by arrays of capillary tubes, by arrayed pipetting devices, or by an array of posts designed to transfer liquid droplets from a tray of reservoirs.

It is preferred that the reactants be introduced to the substrate in a known pattern for purposes of registration. The initial starting position of the reactant should be known in order to correlate this position with the final position once the

substrate size has been reduced to the dimension which will be employed in conducting the assay. Each binding site may include a dye to assist in the correlation between initial starting point and the end point. Preferably, the dye has a different detection mode, e.g., light source, wavelength, etc., than the dye or indicator used for purposes of detecting binding events on the array.

With continuing reference to Figures 4 and 5, after affixation of the reactant(s) to the substrate, preferably the major surface thereof, or in certain instances, after functionalization of the substrate to create linking agents (not depicted), the substrate 12 is relaxed and the surface area of the major surface 14 of the substrate 12 is reduced by the application of energy, such as heat, in the case of oriented films and by the relaxation of the stretching force in the case of elastomeric materials. The number of binding sites 16 before and after size reduction is equivalent. However, the increase in density of reactants, binding sites 16 and linking agents, if present, may be dramatic. The arrays manufactured in accordance with the methods of the present invention are capable of having binding site densities of over 1,000 per cm^2. A preferred density is at least 25,000 per cm^2 and a most preferred density is over 60,000 per cm^2. Accordingly, the methods of the present invention permit the manufacturer to increase the density of binding sites from the initial affixation of reactants to the size reduced state by fairly substantial factors, such as 4, 10, and even over 20. With reference to Figure 4, the area of each binding site 16 can be reduced by these same factors, thereby creating an increased density of reactant 22 at each site. This increased density of reactant 22 is advantageous where an increased signal for detection is desired when conducting an assay, for example when fluorescent, absorbent, or chemiluminescent species are used as reporters.

With respect to oriented films, the reduction is preferably effected by the application of heat. However, any mode that results in the reduction of the surface area of the major surface may be sufficient for purposes of this invention. Preferably, the mode of size alteration, such as the application of heat, does not substantially impair the activity of the reactants. The applicant has demonstrated that fairly high heat may be employed to shrink a substrate having oligonucleotides

affixed thereto (approximately 150 degrees Celsius) without destroying the ability to have subsequent DNA hybridization occur with the oligonucleotides.

With respect to elastomeric materials, the surface area reduction may be achieved by releasing the force that is holding the material in the stretched condition. The substrate may be subsequently treated to hold the substrate in the reduced format. Alternatively, a backing or other physical means may be affixed to the substrate to hold it in the size altered format.

After size alteration of the substrate, the substrate, if desired, may be treated to retain the substrate in the reduced surface area state. Such treatment includes cross-linking the substrate. Alternatively, physical modes may be used, such as affixing a backing to the substrate.

The arrays manufactured by the methods of the present invention are useful in a variety of applications, including without limitation, gene sequencing, monitoring gene expression, gene mapping, disease detection, drug discovery, and combinatorial chemistry.

One skilled in the art will recognize that the methods of the present invention may be adapted for use on a mass production basis.

EXAMPLE 1

Affixation of Pattern to Biaxially Oriented Film

This example serves to demonstrate a method of the present invention using a test pattern printed on a biaxially oriented heat shrink film substrate.

A repeating pattern of circular spots was printed on the surface of a roll of biaxially oriented polyethylene shrink film (Cryovac™ D-955 Film, W.R. Grace & Co., Duncan, South Carolina) using standard flexographic printing methods. The pattern comprised a 34 X 32 square array of circular spots (0.5 mm diameter) spaced 1.0 mm apart center to center (100 spots per square centimeter). Following printing, a section of film containing the pattern was cut from the roll. The film was then placed on a hot plate with a surface temperature of 155°C. The film was occasionally flipped with tweezers to provide even heat distribution during the shrink step. After observable shrinkage had ceased (approximately 2-3 minutes), the film was removed from the hot plate and allowed to cool. The resulting size of the pattern after the shrink step was approximately 0.77 cm x 0.70 cm, with the spots decreased in size to 110 microns in diameter spaced approximately 225 microns apart, as measured under a microscope. The original spot density increased approximately 20 fold, from 100 spots per square centimeter to 2,000 spots per square centimeter.

EXAMPLE 2

Functionalization of Biaxially Oriented Film to Create Linking Agents

This example serves to demonstrate the covalent attachment of a linking agent to the surface of a biaxially oriented shrink film. The linking agent is used for subsequent attachment of reactants.

Carboxylic acid functionality was generated on the surface of polyethylene shrink film (Cryovac™ D-955, 75 gauge, W.R. Grace and Co., Duncan, SC) according to the procedure of Bentjen, et al. (Journal of Applied Polymer Science, Vol. 44, 1992, p. 965), incorporated herein by reference. A 5 cm x 5 cm section of film was immersed in a chromic acid solution ($CrO_3/H_2O/H_2SO_4$) at 72 °C for 1 minute. The sample was washed with water (1x), nitric acid (10%, 1x), and water

(1x). The sample of polyethylene shrink film was allowed to air dry at ambient temperature. Subsequently, it was immersed in a solution of dichloromethane (10 milliliters) containing diisopropylcarbodiimide (80 microliters, 50 mM, Aldrich Chemical Co.) and N-hydroxysuccinimide (60 mg, 50 mM). The solution containing the film was gently agitated for 30 minutes. O.O' Bis (2-aminopropyl)polyethylene glycol 800 (500 mg, Fluka Chemical Co.) was then added along with diisopropylethylamine (20 microliters, Aldrich). The solution was gently agitated for 18 hours at which time the polyethylene shrink film containing a hydrophilic linking amine group was removed and washed with dichloromethane (3x).

A 5 cm x 5 cm section of the polyethylene shrink film prepared as described above was immersed in a solution (5% solids, methylethylketone, 25 ml) containing a copolymer of vinyldimethyl azlactone/dimethylacrylamide (60/40 wt/wt), prepared by typical solution polymerization method well-known in the art, such as that described in US patent 4,304,705. The solution was gently agitated for 2 hours at room temperature.. The polyethylene film was removed from this solution, washed with MEK (15 minutes) and allowed to air dry, thus generating a substrate including covalently attached linking agents.

EXAMPLE 3

Affixation of Reactant to Biaxially Oriented Film

This example demonstrates the covalent attachment of an oligonucleotide to the surface of the film prepared in Example 2.

Fluorescently labeled thymidine octamers were used to demonstrate covalent attachment to the azlactone functionalized film of Example 2. 3'-C3-amino-(thymidine)8-5'-fluorescein isothiocyanate (H_2N-(T)8-FITC) and 3'-hydroxyl-(thymidine)8-5'-fluorescein isothiocyanate (HO-(T)8-FITC) were purchased from Genemed Synthesis, Inc., South San Francisco, CA. The lyophilized samples (5 O.D. ,57 nanomoles) were reconstituted in deionized water (0.5 ml) and stored frozen. Solutions of oligonucleotide (20 nanomole/ml) were

prepared from this stock solution by dilution into phosphate buffer (50 mM, pH 8.5).

The solutions were manually spotted in adjacent rows on the surface of the film using a microcapillary (4 microliter Microcap, Drummond Scientific Co., Broomall, PA) by briefly contacting the surface of the film with the opening of the microcapillary, depositing approximately 50 nanoliters of solution per spot. The spotted film was placed in a covered petri dish overnight (16 hours) at room temperature. Subsequently, the film was placed in a solution of ethanolamine (50 mM in water). After 45 minutes, the film was removed and washed in water (2X) followed by washing (30 minutes) in a solution of phosphate buffered saline containing 0.05% Tween 20. The film was washed again in water (2X), then air-dried. Dust was removed from the surface of the film using a can of Effa Duster™ (Ernest F. Fullam, Inc., Latham, NY). The film was hydrated with pH 7.0 phosphate buffer and observed under a fluorescence microscope equipped with a FITC/TRITC filter set (Chroma Technology). Fluorescence was observed in the row of spots corresponding to the amine-terminated oligonucleotide solution. Each spot was approximately 700 microns in diameter, corresponding to an area of 0.38 mm^2. Extremely faint fluorescence was observed in the row corresponding to the hydroxyl terminated oligonucleotide, thus demonstrating a high degree of covalent attachment of the amine-reactive oligonucleotide with the azlactone linking agent.

A hot plate was heated to a surface temperature of 155°C. To prevent sticking to the metal plate during the shrinkage step, a silicone film (0.040", 3M Co.) was placed on the surface of the hot plate. The film containing attached oligonucleotide was then placed on the silicone film and allowed to shrink. The film was occasionally flipped with a forceps to provide uniform heating. When no further shrinkage was observed, the film was removed from the hot plate and allowed to cool. The film was hydrated with pH 7.0 phosphate buffer and observed under a fluorescence microscope equipped with a FITC/TRITC filter set. After shrinkage, the spot size had been reduced to an area of 0.023 mm^2. Correspondingly, the intensity of the spot is significantly increased due to the

increased local concentration of the labeled octamer, which is further demonstrated in the following examples.

EXAMPLE 4

Introduction of Reactants to Substrate Using Capillary Tubes

This example serves to demonstrate a method of the present invention using aligned capillary tubes for simultaneous affixation of a reactant on a substrate prepared in accordance with Example 2. This example also demonstrates increased concentration of fluorophore at each array site after shrinkage.

A linear assembly of 20 glass capillaries (100 micron inner diameter, 300 microns outer diameter, 500 micron center to center spacing, approximately 300 cm long) was assembled in registration at the proximal ends of the tubes. The distal ends of the capillaries were placed in a solution of 5((5-aminopentyl)thioureidyl) fluorescein (100 micrograms/ml, Molecular Probes, Eugene, OR) in Na2SO4 (1M)/AMPSO (50 millimolar) buffer (pH 9.5). After the capillaries had completely filled, the proximal end of the capillary assembly was briefly contacted to the surface of an azlactone derivitized film prepared as described in Example 2. A small amount of solution was simultaneously deposited from the ends of each capillary onto the surface of the film upon removal of the assembly from the film. The film was then placed in a covered petri dish and allowed to stand overnight (16 hours). The film was washed in phosphate buffer (50 mM, pH 8.5) and allowed to air dry. The film was then placed on a microscope slide, hydrated with a drop of phosphate buffer, and covered with a glass cover slip. The film was observed under a fluorescence microscope as described in Example 3. The microscope was equipped with a CCD camera (Photometrics, Inc.), which was used to quantify the fluorescence intensity of each spot. The intensity was quantified by capturing an image from the CCD followed by importing the signal into image processing software (UTHSCSA Image Tool V. 2.O, University of Texas). The average fluorescence intensity of a spot was determined using the line profile function of the software. Distances were determined using the distance function calibrated against a 100 micron grid.

Before shrinkage, each spot measured approximately 420 microns in diameter, with a center to center spacing of 500 microns. Average fluorescence intensity for the spots was 4940 relative light units (RLU). The film was then shrunk according to the procedure outlined in Example 1. After shrinkage, images were acquired using identical parameters as were used for the pre-shrunk state. Average intensity of the spots had increased to 22,500 RLU, demonstrating an increased concentration of fluorophore within each spot after the shrink step. Correspondingly, the spot size decreased to approximately 90 microns with a center to center spacing of approximately 120 microns.

EXAMPLE 5

Introduction of Reactants to Substrate Using Patterned Posts

This example serves to demonstrate a method of the present invention using an array of posts for the simultaneous transfer and deposition of reactant solution to the surface of the film substrate.

A 6 X 6 array of square posts was machined from a 1 inch X 1 inch aluminum block having the following dimensions: post height = 1.8 mm, width = 0.75 mm, spacing = 4.0 mm center to center. A small notch having an internal angle of approximately 90 degrees was cut from the tip of each post . A tray having circular reservoirs of 3.1 mm diameter, 2.0 mm depth, and 4.0 mm center to center spacing was drilled from a block of polyethylene. A solution of 5((5-aminopentyl)thioureidyl) fluorescein (described above) was placed in each reservoir (12 microliters per reservoir). The tips of the post array were then dipped in the solutions. Upon removal of the array, a small droplet of solution remained on each post tip. The post array was then contacted with the surface of an azlactone functionalized film. The film was allowed to stand, washed, and imaged as described above. The spots were observed to be approximately 800 microns in diameter, with a center to center spacing of 4.0 mm. Average fluorescence intensity was determined to be 3960 RLU. After shrinking the film as described above, the intensity was observed to increase to a relative fluorescence of 19,130

RLU, with a decrease in diameter to approximately 200 microns and a decrease in center to center spacing to approximately 860 microns.

EXAMPLE 6

DNA Hybridization on Heat Shrink Film Substrate After Reduction of Surface Area of Substrate

This example serves to demonstrate DNA hybridization on a modified shrink film containing covalently attached oligonucleotide.

A 2 cm X 2 cm section of azlactone functionalized film was prepared in accordance with Example 2. Solutions of oligonucleotide were prepared as described in Example 3 using the following sequences: 3'-(C3 amino)- TCC TAA GGC CCA ATA- 5' ("match") and 3'-(C3 amino)- CTT CGG AAT TTG GCG- 5' ("mismatch") (Genemed Synthesis). The solutions were spotted in adjacent rows and allowed to react as described in Example 3. After the reaction, the film was placed on a hot plate and allowed to shrink as described in Example 1.

The film was then placed in a solution of 5X SCC (0.75 M NaCl, 0.075 M sodium citrate, pH 7.0) containing L-sarcosine (0.1%), casein (1%), and sodium dodecyl sulfate (0.02%) for 5 minutes. The film was then transferred to a small vial containing 300 microliters of the above solution containing 3'-(FITC)-TAT TGG GCC TTA GGA-5'-OH (15 nanomoles/ml). The hybridization reaction was gently agitated on a rotary mixer for 16 hours at 25 C. The film was removed from the hybridization solution and washed with 5X SCC (2X). The film was then placed on a microscope slide and hydrated with a drop of phosphate buffer (50 millimolar, pH 7.0). A cover slip was placed on the hydrated film.

The film was observed under a fluorescence microscope equipped with a fluorescein filter set. Fluorescence was observed in the row of spots containing immobilized "match" sequence (3'-(C3 amino)- TCC TAA GGC CCA ATA- 5'). No fluorescence was observed in the row corresponding to the "mismatched" sequence (3'-(C3 amino)- CTT CGG AAT TTG GCG- 5'), thus demonstrating that an oligonucleotide can be covalently attached to the surface of a biaxially oriented

film, heat can be applied to shrink the film, and a complimentary oligonucleotide can be hybridized to the oligonucleotide on the resulting film.

EXAMPLE 7

Prophetic Example to Functionalize an Elastomeric Substrate

This example serves to illustrate a method of rendering the surface of an elastomeric rubber substrate chemically reactive.

In this example, a sheet of rubber (obtained from a variety of sources, for example Lloyd Manufacturing, Warren, Rhode Island) may treated to convert a small percentage of double bonds in the polymer backbone to epoxides. For this example the sheet may contain carbon black to reduce background fluorescence. Epoxidization can be achieved via several routes that are well-known in the art, including treatment with perbenzoic, pepthallic, and peracetic acid. It is well-known in the art that epoxides can be ring opened with a variety of nucleophiles, including water, alcohols, hydrogen halides, thiols and amines. Epoxidized rubber, prepared by one of the procedures outlined above may be treated with an excess of O.O' Bis (2-aminopropyl)polyethylene according to the procedure outlined in Example 2. If necessary, the reaction may be heated to promote ring opening of the epoxide. The amine-functionalized rubber may then treated with a copolymer of vinyldimethyl azlactone/dimethylacrylamide as described in Example 2, generating a highly functional surface that is reactive towards nucleophilic moieties, for example amine terminated oligonucleotides. Alternatively, if a lower degree of substitution is needed, the epoxidized rubber may be treated directly with amine terminated oligonucleotide in a single step.

EXAMPLE 8

Prophetic Example of Affixation of Reactant to Elastomeric Substrate

The functionalized elastomeric substrate formed as described in Prophetic Example 7 may be mechanically elongated in either the "x" or "y" direction or simultaneously in both "x" and "y", for example by placing the substrate over a frame or mandrel. Reactants in the form, for example, of oligonucleotides, may be applied to the elongated elastomer. A variety of methods can be employed for forming the array, including delivery through an array of tubes, needles, inkjets, pens, or via transfer from an array of reservoirs using a stamp. After the solutions have been deposited on the surface and the biomolecules have been allowed to react, the mechanical force is removed, thereby reducing the size of the array while at the same time increasing the local concentration of reactants within each site on the array.

EXAMPLE 9

Registration of Reactants on Substrate

This example serves to demonstrate a method for locating the reactants after affixation to a biaxially oriented film using a reporter molecule incorporated within each array site. The reporter molecule used for locating the array elements is detected at a wavelength that is different than the reporter molecule used in the assay.

A solution "1" containing 5-(2-aminoethylamino)-1-napthalene (EDANS, 200 micromolar in pH 8.5 phosphate buffer) was prepared. A second solution "2" containing 3'-C3-amino-(thymidine)8-5'-fluorescein isothiocyanate (H_2N-(T)8-FITC) was prepared by dilution of the stock solution from example 3 into the EDANS solution "1" (5 micromolar final H_2N-(T)8-FITC concentration.) Rows of spots from solution "1" were generated on the film using a microcapillary spotter as described in Example 3. Within each row, a random space was left open, which was subsequently spotted with solution "2". In this manner rows of spots were generated where all spots contained EDANS and one spot contained EDANS plus attached fluorescein-labeled oligonucleotide. The spotted film was placed in a

covered petri dish for one hour, at which time it was removed and washed with water, dried, and shrunk as described in Example 1. After the shrink step, the film was observed under a fluorescence microscope first using a bandpass excitation filter (350 +/- 20 nm) and a longpass emission filter set (>420 nm, Chroma Technology). Using this filter set, EDANS fluorescence from each spot was observed and the image and position of each spot recorded using a CCD camera and imaging software as outlined in Example 4. The film was then observed using a FITC/TRITC filter set (Chroma Technology). Only the single spots within each row containing attached H_2N-(T)8-FITC were observed. An "overlay" of the two images provides the location of the spots containing the labeled oligonucleotide, thus demonstrating that a reporter molecule can be incorporated into each array element, serving to determine the spatial location of each spot in the array. This information is then stored and used to determine the identity of the of spots in which a second reporter is located, for example a reporter bound at an array site to sites during a hybridization reaction.

EXAMPLE 10

Preparation of Copolymers Comprising Linking Agents

Preparation of copolymers is readily accomplished by procedures well known in the art, such as procedures taught in U.S. Patent 4,304,705. The following is a typical example: Into a reaction vessel equipped with a stirrer, thermometer, reflux condenser, means for heating, and means for maintaining a nitrogen atmosphere in the vessel were charged (parts by weight) 2-vinyl-4,4-dimethyl-2-oxazolin-5-one (vinyldimethylazlactone 12 parts), N,N-dimethylacrylamide (28 parts), 2-butanone (60 parts) and azobisisobutyronitrile (0.15 parts). The solution was sparged with nitrogen and heated at 55°C with agitation for 24 hours. After this time the percent polymer solids in the solution obtained, as determined by a standard gravimetric procedure, was 39.8%, indicative of 100% conversion of monomers to polymer. This polymer solution was then diluted to lower % solids solutions with additional 2-butanone or other solvents for the preparation of coating solutions.

In a similar manner, other polymers having different ratios of monomers, different comonomers, or different linking agent monomers can be prepared and used in the invention.

EXAMPLE 11

Priming and Coating Methods

This example serves to demonstrate methods for priming the surface of substrate as well as methods for providing uniform, thin coatings comprising linking agents on the substrates.

For the Examples 11a-11i described in Table 1, a roll of oriented substrate film was either unprimed (none), corona treated (Cr), or ammonia-plasma treated (AP) according to techniques well known in the art prior to coating. Priming with Polyethylenimine (PEI, average M_w ca. 750,000, 50 wt. % solution in water) (Aldrich) was accomplished by diluting the stock solution to 0.05 % w/w with methanol followed by extrusion die coating onto the appropriate film substrate.

For coating, the copolymers comprising linking agents prepared as described in Example 10 were diluted with appropriate solvents to provide the coating solutions, typically less than 10 % solids by weight, preferably <5 % solids. Coating methods used were: (1) Extrusion die coating, "E"; and (2) Reverse-roll gravure, "G". Optionally, the coating solution was formulated with a cross-linker prior to coating. For extrusion coating, this was accomplished by utilizing two reservoirs, one for the polymer solution and one for the crosslinker solution. The solutions were pumped through an in line mixer just prior to entering the coating die. For each example, the solvent was removed from the coating by passage of the film through an oven heated to 38° C for approximately 1 minute.

Table 1

Exp.	Substrate	Priming	Copolymer Coatings used	Solvent (% Solids)	Coating Method	Crosslinker (wt. %)
11a	A	None	70:30 p(DMA/VDM)	MEK (1.5)	E	ED (10%)
11b	A	Cr	70:30	MEK (1.0)	E	ED (10%)

			p(DMA/VDM)			
11c	A	Cr	70:30 p(DMA/VDM)	MEK (1.5)	E	ED (10%)
11d	B	AP	70:30 p(DMA/VDM)	IPA (5.0)	G	None
11e	A	None	50:30:20 p(BA/DMA/VDM)	MEK (1.5)	E	None
11f	B	Cr	70:30 p(DMA/VDM)	IPA (1.0)	G	None
11g	B	None	70:30 p(DMA/VDM)	IPA (1.0)	G	None
11h	A	Cr/PEI	70:30 p(DMA/VDM)	MEK (1.5)	E	None
11i	C	Cr	70:30 p(DMA/VDM)	MEK (1.0)	E	ED (2.5%)

A = Biaxially oriented polyethylene, Cryovac D955 1.0 mil, Sealed Air Co., Duncan, SC.

B = Biaxially oriented polyethylene, Cryovac D955 0.6 mil, Sealed Air.

C = Biaxially oriented polyethylene, Clysar 1.0 mil, DuPont Co., Wilmington, DE.

Copolymers: DMA = dimethylacrylamide; VDM = vinyldimethylazlactone; BA = butyl acrylate

Solvents: MEK = 2-butanone; IPA = isopropyl alcohol

Cross-linker: ED = 1,2-ethylenediamine (Aldrich);

Other abbreviations described in Methods above

EXAMPLE 12

Formation of Undulated Surface

This example serves to demonstrate the formation of undulated surfaces from a coating comprising linking agents on the substrate.

A section of coated film from Example 11a was relaxed according to the procedure outlined in Example 3. SEM images were obtained using standard preparation techniques (scanning electron microscope, Model XL 30 Series, Philips Electronic Instruments, Mahwah, NJ). Briefly, the samples were placed on a small amount of carbon tape on the mounting stub so that it contacted only the underside of the sample at opposing corners. The mounted samples were then placed in a sputter chamber (Hummer XP, Anatech LTD) for a time sufficient to deposit approximately 7-9 nm of gold coating. Samples were examined under an accelerating voltage of 15kV at a spot size of 4 with the samples at a 40 degree tilt. Images for a sample having an oriented and a relaxed substrate sample thereof were obtained (Figure 6a and 6b, respectively). Figure 6a shows that the coating comprising linking agents is substantially smooth prior to shrinking. Figure 6b demonstrates that the linking agent coating has formed an undulated surface. Examples 11b, 11c, 11d, 11f, 11g, 11h, 11i were also shown to form undulated surfaces.

EXAMPLE 13

Stability of Coatings

This example serves to demonstrate improved adhesion of the linking agent coating subsequent to relaxation of the substrate.

Stability of coatings on coated sample of Example 11c with respect to washings at high pH, high temperatures, and in the presence of surfactants was studied in the following manner.

A 50 mM sodium phosphate buffer was prepared at pH 8.38 with 1% (*w/w*) sodium dodecyl sulfate (SDS) in DI water. Oriented and relaxed pieces of the above sample were immersed in the above buffer solution at 80°C for 5 hours.

The samples were analyzed using attenuated total reflectance (ATR) (Model Bomem MB 102, Golden Gate Diamond ATR Series, Graseby Specac) IR spectroscopy to detect the presence of the coating. The relaxed sample contained the following absorbance bands consistent with the presence of copolymer coating: 1618 (strong, broad band due to amide carbonyl), 1498, 1398, 1355 (medium, sharp bands) cm^{-1}. These bands were absent in the oriented sample, thus indicating that the process of relaxing using heat, improves the adhesion of the coating to the substrate under these conditions.

EXAMPLE 14

PEI Coating

This example serves to demonstrate a method for making a PEI undulated coating.

A sample of oriented film (Cryovac D955, 1.0 mil) was corona (Cr) treated and coated with a 0.05% (*w/w*) solution of PEI in methanol (Aldrich) as described in Example 11. A section of this sample was relaxed according to the procedure outlined in Example 3. The SEM of the coating is shown in figure 7a, demonstrating that the coating is substantially smooth. Accordingly, an undulated surface did not form.

In order to prepare a PEI surface that was undulated, the azlactone/dimethylacrylamide coated substrate of Example 11a was extrusion over-coated with a 0.3% (w/w) solution of linear Polyethylenimine (PEI M_n ca. 423) (Aldrich) in methanol. A section of this sample was relaxed according to the procedure outlined in Example 3. The SEM of this multilayer coating is shown in Figure 7b, demonstrating that the coating of PEI linking agent is present in an undulated surface.

EXAMPLE 15

Carboxylated Polyvinylchloride Coating

This example demonstrates an additional polymer coating containing linking agents that formed the undulated surface of the present invention.

A 1 % (*w/w*) solution of carboxylated polyvinylchloride (1.8% carboxylated) (Aldrich) was made in tetrahydrofuran (THF) (Aldrich), with and without 1% DI water. These two solutions were hand-coated on the shrink film (Cryovac D955, 1.0 mil) at a wet of thicknesses of 0.005 inch, 125 microns. After coating the solvent was allowed to evaporate at room temperature for approximately 20 minutes. The oriented and relaxed samples for the samples coated without water were analyzed using SEM techniques. The micrographs showed that before relaxation, a smooth coating was present (Figure 8a), whereas after relaxation an undulated surface was observed (Figure 8b). The coating formed from the solution containing water also formed undulations.

EXAMPLE 16

Variation of Polymer Glass Transition Temperature

This example serves to demonstrate that a polymer containing linking agents having a glass transition temperature substantially lower than the glass transition (T_g) temperature of the substrate may not form undulations.

A section of the coated film of example 11e was relaxed according to the procedure outlined in Example 3. The (T_g) of the copolymer used in this example was calculated to be approximately 0°C. The SEM of the coating is shown in Figure 9a, demonstrating that the low T_g copolymer forms a substantially smooth surface. In comparison, Figure 9b depicts the SEM of the relaxed film of example 11d, where the T_g of the copolymer was measured to be 110° C by modulated differential scanning calorimetry (MDSC 2920, TA Instruments, Inc., New Castle, DE). This sample formed an undulated surface.

EXAMPLE 17

Comparison of Oligonuclotide Hybridization on Glass Microscope Slides and Coated Shrink Film.

This example demonstrates enhanced signal obtained during an oligonucleotide hybridization utilizing a coated film of the present invention.

The procedure of Guo et. al. (Nucleic Acids Research, 1994, Vol. 22, No. 24) was used to prepare a reactive surface on a glass microscope slide. A slide treated with aminopropyltrimethoxy silane (Newcomer Supply, Middletown, WI) was immersed in 1,4 phenylene diisothiocyanate (0.2% solution in 1:9 pyridine:dimethylformamide). After two hours, the slide was rinsed with methanol (2X) and acetone (2X) followed by air drying. Two sections (1 inch by 1 inch) of shrink film coated with azlactone/dimethylacrylamide copolymer as described in Example 11c were used in the subsequent steps.

Solutions of the three oligonucleotides (Genosys, The Woodlands, TX, 250 mM in AMPSO buffer, pH 9.0) were prepared as described in Example 4 followed by spotting in adjacent rows using a capillary tube as described in Example 3 (Row 1 = FITC labeled, row 2 = "match", row 3 = "mismatch"). After spotting, the glass and film samples were placed in a covered, humidified petri dish. After two hours, the samples were rinsed with distilled water, AMPSO buffer (50 mM, pH 9.0), distilled water, SDS (0.1% in water), and distilled water. One of the shrink film samples was relaxed according to the procedure in Example 1. FITC labeled oligonucleotide complimentary to the immobilized "match" row of spots was hybridized to the glass, oriented film, and relaxed film according to the procedure in Example 6 by placing a small drop of the hybrizidation solution onto each sample followed by addition of a cover slip. The samples were allowed to hybridize for 30 minutes in a 45° C incubator. After hybridization, the samples were rinsed as described above. Fluorescence intensity for each row of spots was measured using a raster scanning device equipped with a 488 nanometer laser, fluorescein filters, and a photomultiplier tube. Average intensities expressed as relative light units (RLU) were measured. Detector gain adjustments were necessary for the film samples, which saturated the detector under the conditions used to measure the glass slide. A gain-dependent conversion factor was used to calculate normalized RLU values for the three samples. The following table summarizes the results of this experiment. The results clearly show an increase in intensity for the coated film samples due to a higher concentration of reactants. A

5 further 10X enhancement results from relaxing the sample due to increased density of reactants.

sample	**Row 1- FITC labeled (RLU)**	**Row 2- "match" (RLU)**	**Row 3- "mismatch" (RLU)**
Glass microscope slide	198	75	No signal
Unshrunk film	15,100	14,100	No signal
Shrunk film	165,000	162,000	No signal

10

WHAT IS CLAIMED IS:

1. An array, comprising:

a polymeric substrate;

a coating comprising linking agents at least partially adhered to said substrate; and

a reactant affixed to said linking agents to form binding sites, wherein said coating comprising linking agents has a projected surface area and a topographical surface area and said topographical surface area is greater than said projected surface area.

2. The array of claim 1 wherein said coating comprising linking agents comprises an undulated surface.

3. The array of claims 1 and 2 wherein said topographical surface area is at least two times greater than said projected surface area.

4. The array of claims 1, 2, and 3 wherein said array includes a binding site density of over 2,000 binding sites per square centimeter.

5. A material for use in the manufacturing the array of claim 1, comprising:

an oriented polymeric substrate and a coating of linking agents at least partially adhered thereto.

6. A method of manufacturing the array of claim 1, comprising:

providing an oriented polymeric substrate;

applying a coating comprising linking agents on said polymeric substrate;

affixing reactants thereto to form binding sites; and

relaxing the substrate, wherein the coating has a topographical surface area and a projected surface area and said topographical surface area is greater than said projected surface area.

7. The method of claim 6 wherein said coating forms an undulated surface.

8. A method of manufacturing an array such as the array of claim 1, comprising:

a. affixing a reactant to an oriented polymeric substrate including a major surface with a surface area to create binding sites on said substrate; and

b. reducing the surface area of said major surface by heating said polymeric substrate, thereby increasing the density of binding sites on said substrate.

9. A method of functionalizing a substrate for use in the method of claim 8, comprising functionalizing an oriented film substrate, thereby creating linking agents on said substrate for subsequent affixation of a reactant thereto.

10. A method of functionalizing a substrate for use in the method of claim 8, comprising:

a. stretching an elastomeric material having at least one major surface with a surface area; and

b. functionalizing the major surface, thereby creating linking agents on said substrate for ultimate affixation of a reactant.

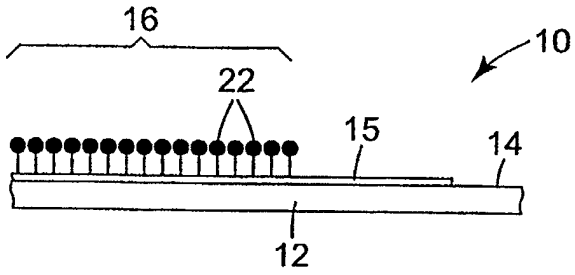

Fig. 1a

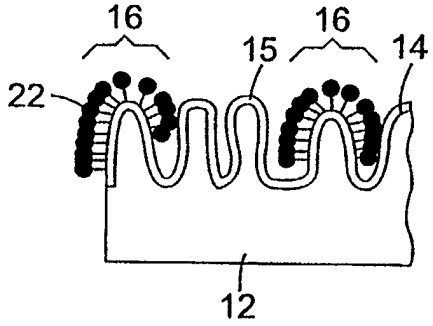

Fig. 1b

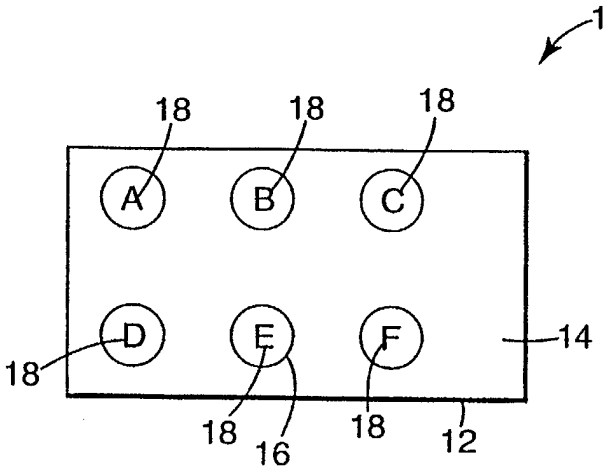

Fig. 2

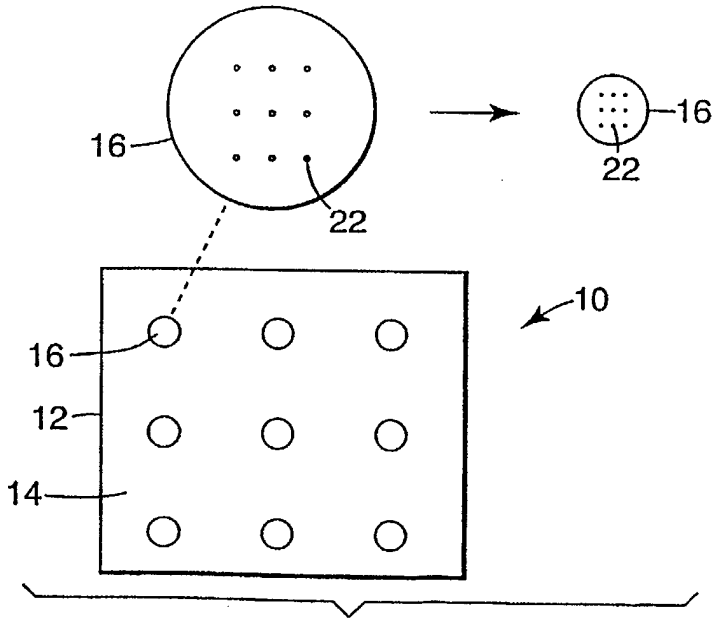

Fig. 3

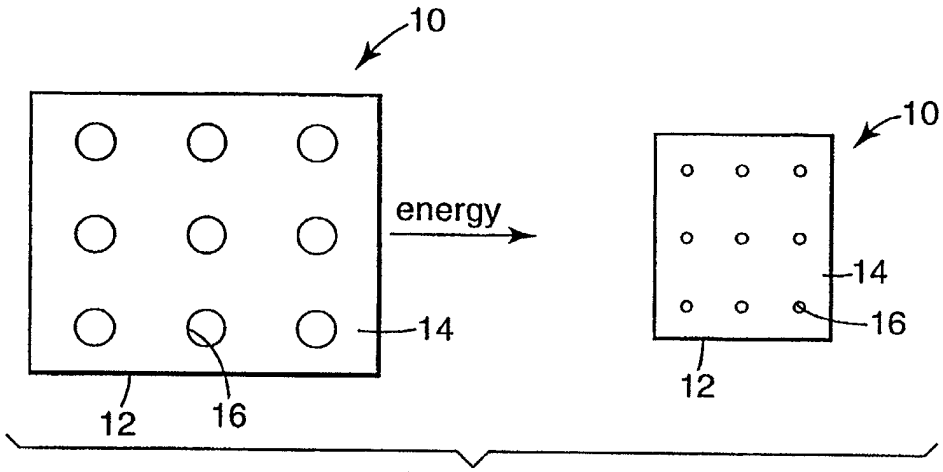

Fig. 4

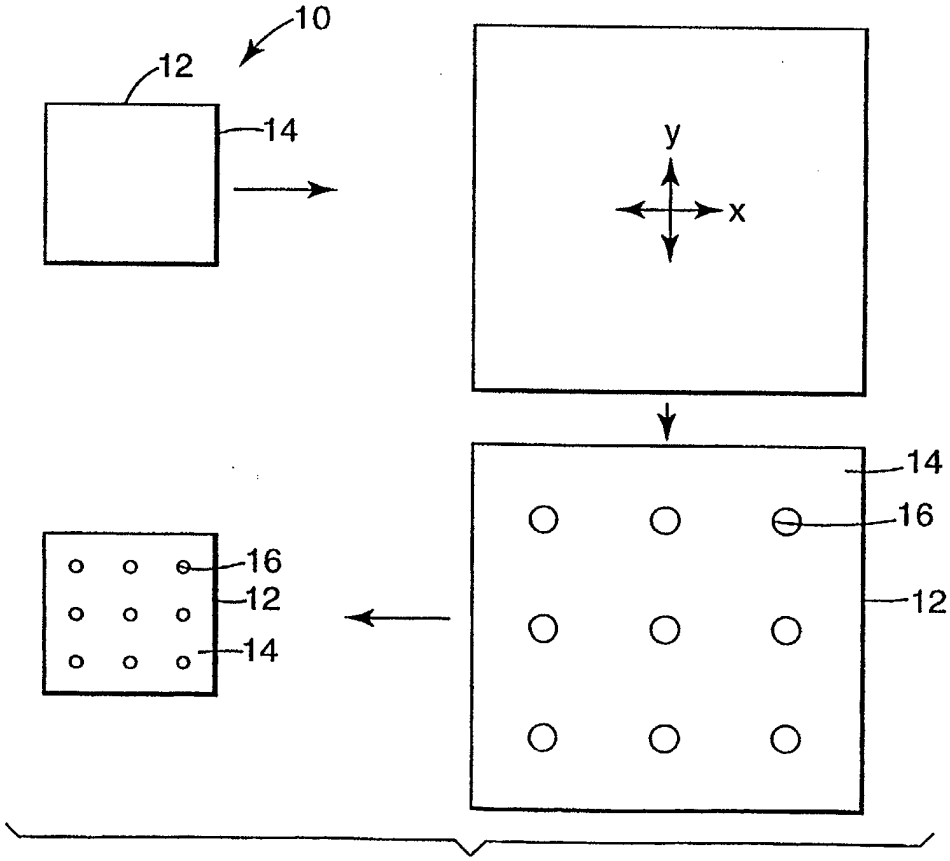

Fig. 5

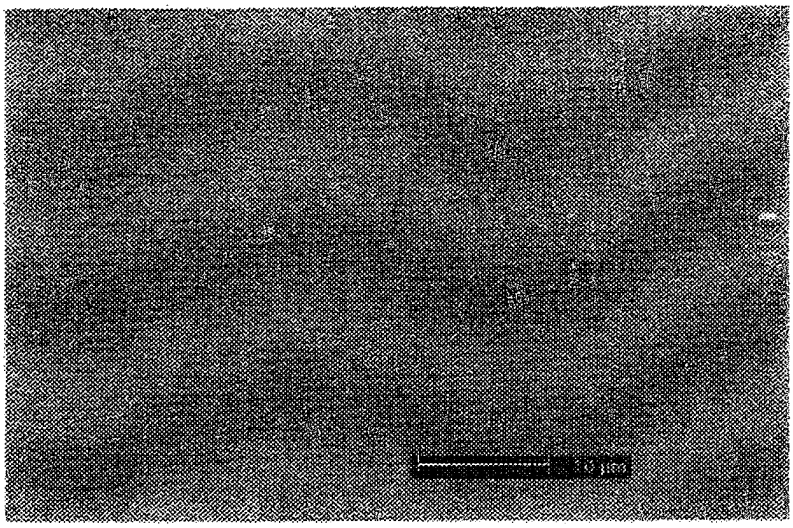

Fig. 6a

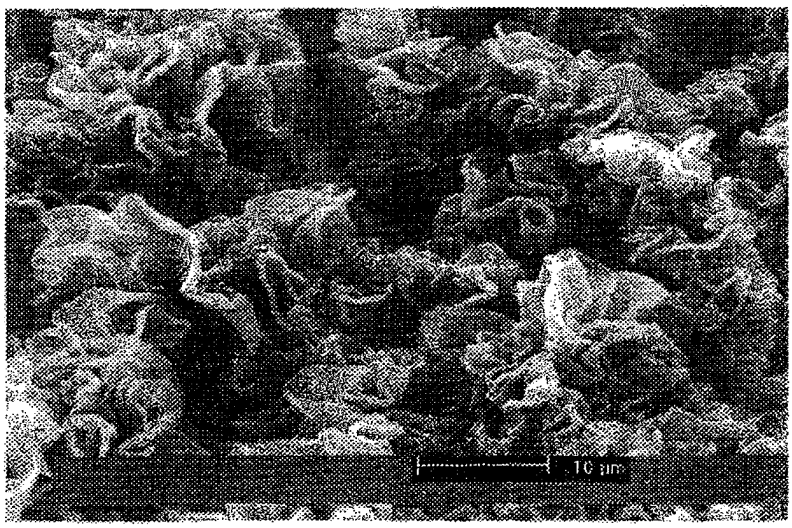

Fig. 6b

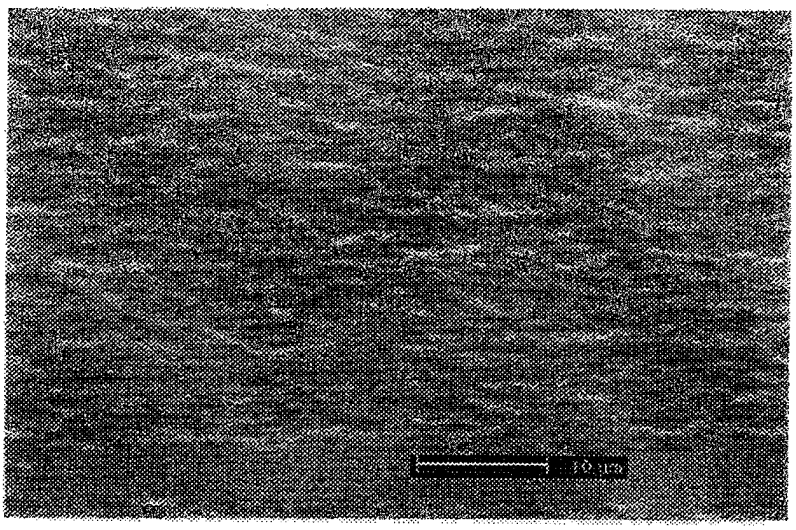

Fig. 7a

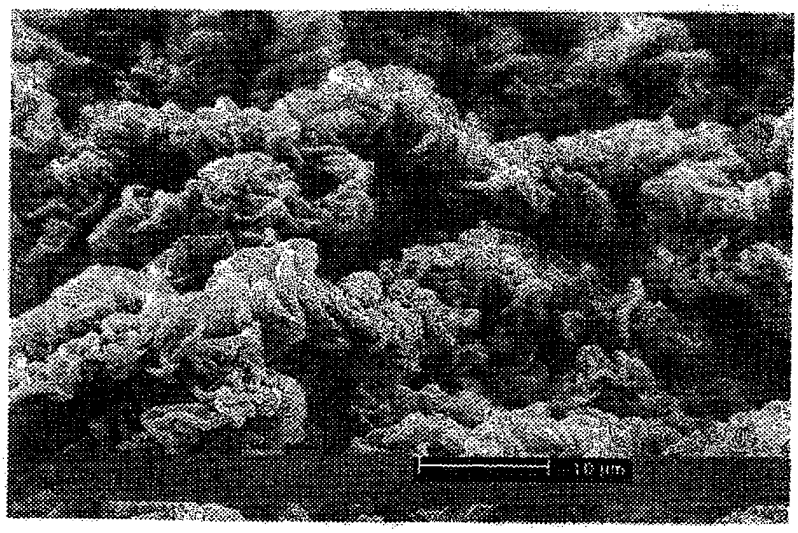

Fig. 7b

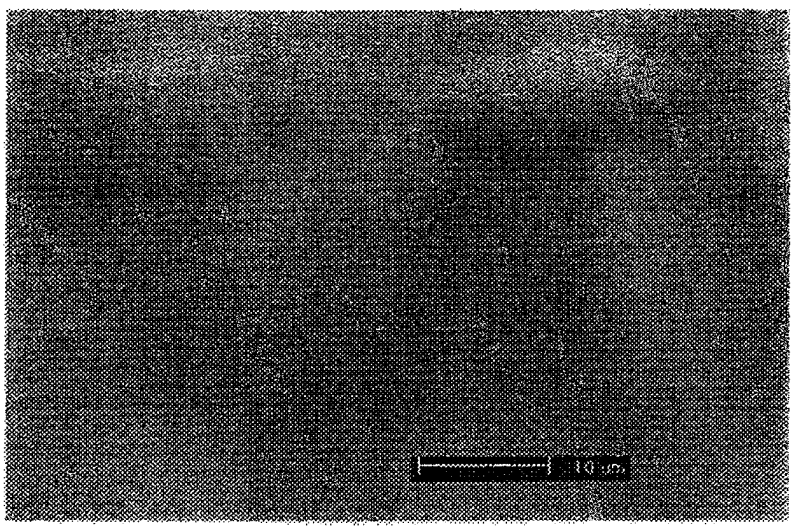

Fig. 8a

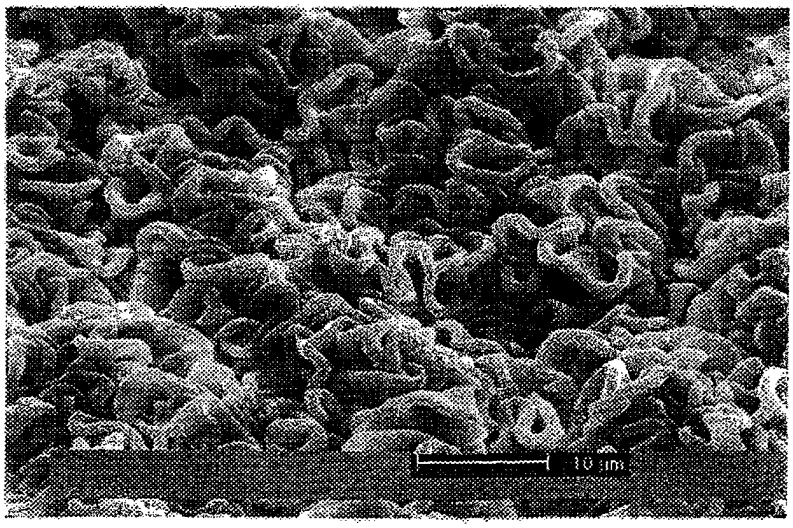

Fig. 8b

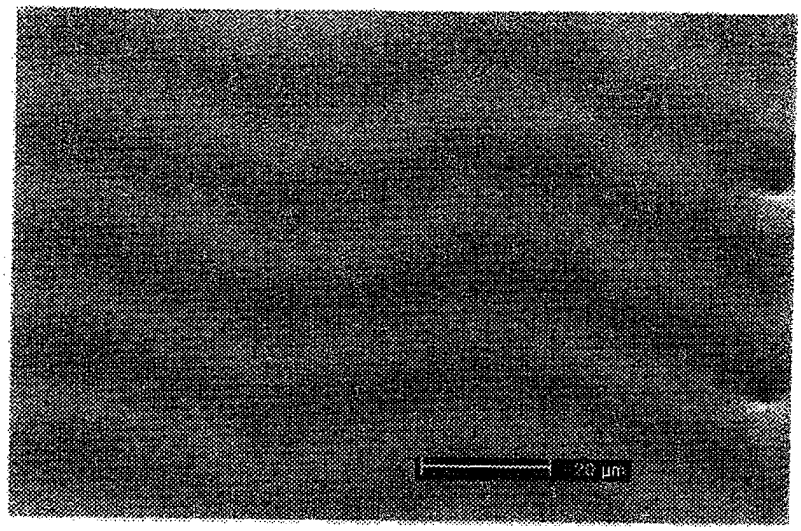

Fig. 9a

Fig. 9b

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(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133–3427 (US).

(72) Inventors: HALVERSON, Kurt, J.; P.O. Box 33427, Saint Paul, MN 55133–3427 (US). PATIL, Sanjay, L.; P.O. Box 33427, Saint Paul, MN 55133–3427 (US). RASMUSSEN, Jerald, K.; Post Office Box 33427, Saint Paul, MN 55133–3427 (US).

(74) Agents: ROGERS, James, A. et al.; Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133–3427 (US).

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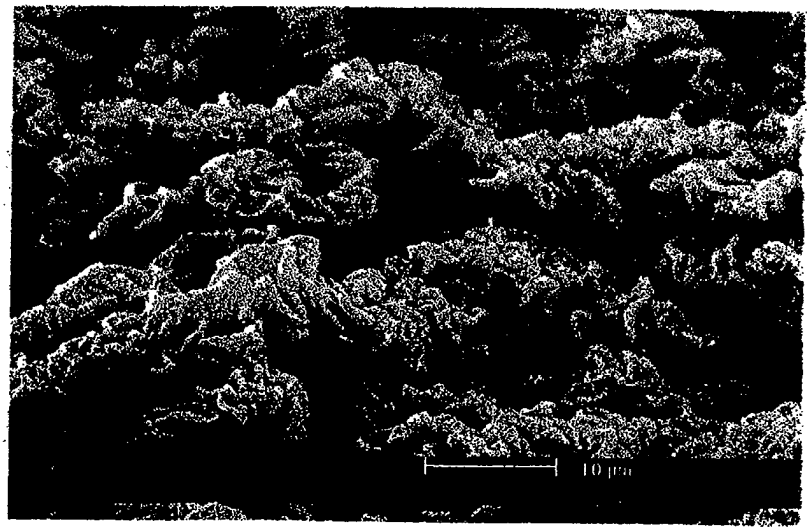
(57) Abstract

High–density, miniaturized arrays including high surface areas. Arrays described include substrate with a coating of linking agents, as well as arrays with reactants affixed to the substrates. Methods of manufacturing high–density arrays of reactants. The methods include the use of oriented, heat shrink films and elastomeric materials. Methods of functionalizing a substrate with linking agents for subsequent affixation of reactants are also disclosed herein.



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Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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APPENDIX VIII.

Serial No.: 09/819,317

Docket No.: 56066US002

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1. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

2. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied 105 S. Ct. 172, on remand 670 F. Supp. 760, 3 USPQ2d 1511, affirmed in part and reversed in part 842 F.2d 1275, 6 USPQ2d 1277.

3. *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

4. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

5. *In re Vacek*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

6. M.P.E.P. §706.02(j) (8th Edition, 1st Revision).

7. M.P.E.P. §2141.01 (8th Edition, 1st Revision).

8. M.P.E.P. §2143.03 (8th Edition, 1st Revision).

Intellectual Property Library ISSN 1526-8535

FULL TEXT OF CASES (USPQ2D)
All Other Cases

In re Fine (CA FC) 5 USPQ2d 1596 In re Fine

U.S. Court of Appeals Federal Circuit
5 USPQ2d 1596

Decided January 26, 1988
No. 87-1319

Headnotes

PATENTS

1. Patentability/Validity -- Obviousness -- Evidence of (§ 115.0903)

Patent and Trademark Office improperly rejected claimed invention for obviousness since nothing in cited references, either alone or in combination, suggests or teaches claimed invention, since there is consequently no support for PTO's conclusion that substitution of one type of detector for another in prior art system, resulting in claimed invention, would have been obvious, and since PTO therefore failed to satisfy its burden of establishing prima facie case of obviousness by showing some objective teaching or generally available knowledge that would lead one skilled in art to combine teachings of existing references.

2. Patentability/Validity -- Obviousness -- In general (§ 115.0901)

Obviousness is tested by what combined teachings of prior art references would have suggested to those of ordinary skill in art, not by whether particular combination of elements from such references might have been "obvious to try."

3. Patentability/Validity -- Obviousness -- Evidence of (§ 115.0903)

Patent and Trademark Office erred, in rejecting as obvious system for detecting and measuring minute quantities of nitrogen compounds, by failing to recognize that appealed claims can be distinguished over combination of prior art references, in view of evidence demonstrating that prior art does not teach claimed temperature range, despite some overlap of preferred temperature ranges for claimed invention and prior art, since purposes of preferred temperature ranges are different and overlap is mere happenstance.

4. Patentability/Validity -- Obviousness -- In general (§ 115.0901)

Dependent claims are non-obvious under 35 USC 103 if claims from which they depend are non-obvious.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences.

Application for patent by David H. Fine, Serial No. 512,374. From decision of Board of Patent Appeals and Interferences affirming rejection of application, applicant appeals. Reversed; Smith, circuit judge, dissenting with opinion.

Attorneys:

Morris Relson and Darby & Darby, New York, N.Y., (Beverly B. Goodwin with them on the brief) for appellant.

Lee E. Barrett, associate solicitor, Arlington, Va., (Joseph F. Nakamura, solicitor, and Fred E. McKelvey, deputy solicitor, with him on the brief) for appellee.

Judge:

Before Friedman, Smith, and Mayer, circuit judges.

Opinion Text

Opinion By:
Mayer, J.

David H. Fine appeals from a decision of the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office (Board) affirming the rejection of certain claims of his application, Serial No. 512,374, and concluding that his invention would have been obvious to one of ordinary skill in the art and was therefore unpatentable under 35 U.S.C. §103. We reverse.

Background

A. *The Invention .*

The invention claimed is a system for detecting and measuring minute quantities of nitrogen compounds. According to Fine, the system has the ability to detect the presence of nitrogen compounds in quantities as minute as one part in one billion, and is an effective means to detect drugs and explosives, which emanate nitrogen compound vapors even when they are concealed in luggage and closed containers.
The claimed invention has three major components: (1) a gas chromatograph which separates a gaseous sample into its constituent parts; (2) a converter which converts the nitrogen compound effluent output of the chromatograph into nitric oxide in a hot, oxygen-rich environment; and (3) a detector for measuring the level of nitric oxide. The claimed invention's sensitivity is achieved by combining nitric oxide with ozone to produce nitrogen dioxide which concurrently causes a detectable luminescence. The luminescence, which is measured by a visual detector, shows the level of nitric oxide which in turn is a measure of nitrogen compounds found in the sample.
The appealed claims were rejected by the Patent and Trademark Office (PTO) under 35 U.S.C. §103. Claims 60, 63, 77 and 80 were rejected as unpatentable over Eads, Patent No. 3,650,696 (Eads) in view of Warnick, et al., Patent No. 3,746,513 (Warnick). Claims 62, 68, 69, 79, 85 and 86 were rejected as unpatentable over Eads and Warnick in view of Glass, et al., Patent No. 3,207,585 (Glass).

B. *The Prior Art .*

1. *Eads Patent .*

Eads discloses a method for separating, identifying and quantitatively monitoring sulfur compounds. The Eads system is used primarily in "air pollution control work in the scientific characterization of odors from sulfur compounds."
The problem addressed by Eads is the tendency of sulfur compounds "to adhere to or react with the surface materials of the sampling and analytical equipment, and/or react with the liquid or gaseous materials in the equipment." Because of this, the accura

cy of measurement is impaired. To solve the problem, the Eads system collects an air sample containing sulfur compounds in a sulfur-free methanol solution. The liquid is inserted into a gas chromatograph which separates the various sulfur compounds. The

compounds are next sent through a pyrolysis furnace where they are oxidized to form sulfur dioxide. Finally, the sulfur dioxide passes through a measuring device called a microcoulometer which uses titration cells to calculate the concentration of sulfur compounds in the sample.

2. *Warnick Patent .*

Warnick is directed to a means for detecting the quantity of pollutants in the atmosphere. By measuring the chemiluminescence of the reaction between nitric oxide and ozone, the Warnick device can detect the concentration of nitric oxide in a sample gaseous mixture. Warnick calls for "continuously flowing" a sample gaseous mixture and a reactant containing ozone into a reaction chamber. The chemiluminescence from the resulting reaction is transmitted through a light-transmitting element to produce continuous readouts of the total amount of nitric oxide present in the sample.

3. Glass Patent.

The invention disclosed in Glass is a device for "completely burning a measured amount of a substance and analyzing the combustion products." A fixed amount of a liquid petroleum sample and oxygen are supplied to a flame. The flame is then spark-ignited, causing the sample to burn. The resulting combustion products are then collected and measured, and from this measurement the hydrogen concentration in the sample is computed.

C. *The Rejection .*

The Examiner rejected claims 60, 63, 77 and 80 because "substitution of the [nitric oxide] detector of Warnick for the sulfur detector of Eads would be an obvious consideration if interested in nitrogen compounds, and would yield the claimed invention." He further asserted that "Eads teaches the [claimed] combination of chromatograph, combustion, and detection, in that order. . . . Substitution of detectors to measure any component of interest is well within the skill of the art." In rejecting claims 62, 68, 69, 79, 85 and 86, the Examiner said, "Glass et al. teach a flame conversion means followed by a detector, and substitution of the flame conversion means of Glass et al. for the furnace of Eads would be an obvious equivalent and would yield the claimed invention." The Board affirmed the Examiner's rejection.

Discussion

A. *Standard of Review .*

Obviousness under 35 U.S.C. §103 is " 'a legal conclusion based on factual evidence.' " *Stratoflex, Inc. v. Aeroquip Corp .*, 713 F.2d 1530, F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983) (quoting *Stevenson v. Int'l Trade Comm'n* , 612 F.2d 546, 549, 204 USPQ 276, 279 (CCPA 1979)). Therefore, an obviousness determination is not reviewed under the clearly erroneous standard applicable to fact findings, *Raytheon Co. v. Roper Corp .*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983); it is "reviewed for correctness or error as a matter of law." *In re De Blauwe* , 736 F.2d 699, 703, 222 USPQ 191, 195 (Fed. Cir. 1984).

To reach a proper conclusion under §103, the decisionmaker must step backward in time and into the shoes worn by [a person having ordinary skill in the art] when the invention

was unknown and just before it was made. In light of *all* the evidence, the decisionmaker must then determine whether . . . the claimed invention as a whole would have been obvious at *that* time to *that* person. 35 U.S.C. §103. The answer to that question partakes more of the nature of law than of fact, for it is an ultimate conclusion based on a foundation formed of all the probative facts.
Panduit Corp. v. Dennison Mfg. Co ., 810 F.2d 1561, 1566, 1 USPQ2d 1593, 1595-96 (Fed. Cir. 1987).

B. *Prima Facie Obviousness* .

Fine says the PTO has not established a *prima facie* case of obviousness. He contends the references applied by the Board and Examiner were improperly combined, using hindsight reconstruction, without evidence to support the combination and in the face of contrary teachings in the prior art. He argues that the appealed claims were rejected because the PTO thought it would have been "obvious to try" the claimed invention, an unacceptable basis for rejection.
[1] We agree. The PTO has the burden under section 103 to establish a *prima facie* case of obviousness. *See In re Piasecki* , 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-87 (Fed. Cir. 1984). It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Lalu* , 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984); *see also Ashland Oil, Inc. v. Delta Resins & Refractories, Inc* .,

776 F.2d 281, 297 n.24, 227 USPQ 657 , 667 n.24 (Fed. Cir. 1985); *ACS Hosp. Sys., Inc. v. Montefiore Hosp* ., 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). This it has not done. The Board points to nothing in the cited references, either alone or in combination, suggesting or teaching Fine's invention.
The primary basis for the Board's affirmance of the Examiner's rejection was that it would have been obvious to substitute the Warnick nitric oxide detector for the Eads sulfur dioxide detector in the Eads system. The Board reiterated the Examiner's bald assertion that "substitution of one type of detector for another in the system of Eads would have been within the skill of the art," but neither of them offered any support for or explanation of this conclusion.
Eads is limited to the analysis of sulfur compounds. The particular problem addressed there is the difficulty of obtaining precise measurements of sulfur compounds because of the tendency of sulfur dioxide to adhere to or react with the sampling analytic equipment or the liquid or gaseous materials in the equipment. It solves this problem by suggesting that the gaseous sample containing sulfur compounds be absorbed into sulfur-free methanol and then inserted into a gas chromatograph to separate the sulfur compounds. There is no suggestion in Eads, which focuses on the unique difficulties inherent in the measurement of sulfur, to use that arrangement to detect nitrogen compounds. In fact, Eads says that the presence of nitrogen is undesirable because the concentration of the titration cell components in the sulfur detector is adversely affected by substantial amounts of nitrogen compounds in the sample. So, instead of suggesting that the system

be used to detect nitrogen compounds, Eads deliberately seeks to avoid them; it warns against rather than teaches Fine's invention. *See W. L. Gore & Assoc. v. Garlock, Inc .*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983) (error to find obviousness where references "diverge from and teach away from the invention at hand"). In the face of this, one skilled in the art would not be expected to combine a nitrogen-related detector with the Eads system. Accordingly, there is no suggestion to combine Eads and Warnick.
Likewise, the teachings of Warnick are inconsistent with the claimed invention, to some extent. The Warnick claims are directed to a gas stream from engine exhaust "continuously flowing the gaseous mixtures into the reaction chamber" to obtain "continuous readouts" of the amount of nitric oxide in the sample. The other words, it contemplates measuring the total amount of nitric oxide in a continuously flowing gaseous mixture of unseparated nitrogen constituents. By contrast, in Fine each nitrogen compound constituent of the gaseous sample is retained in the Chromatograph for an individual time period so that each exists in discrete, time-separated pulses. * By this process, each constituent may be both identified by its position in time sequence, and measured. The claimed system, therefore, diverges from Warnick and teaches advantages not appreciated or contemplated by it.
Because neither Warnick nor Eads, alone or in combination, suggests the claimed invention, the Board erred in affirming the Examiner's conclusion that it would have been obvious to substitute the Warnick nitric oxide detector for the Eads sulfur dioxide detector in the Eads system. *ACS Hosp. Sys .*, 732 F.2d at 1575-77, 221 USPQ at 931-33. The Eads and Warnick references disclose, at most, that one skilled in the art might find it obvious to try the claimed invention. But whether a particular combination might be "obvious to try" is not a legitimate test of patentability. *In re Geiger* , 815 F.2d 868, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); *In re Goodwin* , 576 F.2d 375, 377, 198 USPQ 1, 3 (CCPA 1978).
[2] Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller* , 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). But it "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hosp. Sys .*, 732 F.2d at 1577, 221 USPQ at 933. And "teachings of references can be combined *only* if there is some suggestion or incentive to do so." *Id* . Here, the prior art contains none.
Instead, the Examiner relies on hindsight in reaching his obviousness determination.

But this court has said, "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W. L. Gore* , 721 F.2d at 1553, 220 USPQ at 312-13. It is essential that "the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made . . . to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *Id* . One cannot use hindsight reconstruction to pick and choose among isolated

disclosures in the prior art to deprecate the claimed invention.

C. *Advantage Not Appreciated by the Prior Art .*

[3] The Board erred not only in improperly combining the Eads and Warnick references but also in failing to appreciate that the appealed claims can be distinguished over that combination. A material limitation of the claimed system is that the conversion to nitric oxide occur in the range of 600°C to 1700°C. The purpose of this limitation is to prevent nitrogen from other sources, such as the air, from being converted to nitric oxide and thereby distorting the measurement of nitric oxide derived from the nitrogen compounds of the sample.

The claimed nitric oxide conversion temperature is not disclosed in Warnick. Although Eads describes a preferred temperature of 675°C to 725°C, the purpose of this range is different from that of Fine. Eads requires the 675°C to 725°C range because it affords a temperature low enough to avoid formation of unwanted sulfur trioxide, yet high enough to avoid formation of unwanted sulfides. Fine's temperature range, in contrast, does not seek to avoid the formation of sulfur compounds or even nitrogen compounds. It enables the system to break down the nitrogen compounds of the sample while avoiding the destruction of background nitrogen gas. There is a partial overlap, of course, but this is mere happenstance. Because the purposes of the two temperature ranges are entirely unrelated, Eads does not teach use of the claimed range. *See In re Geiger* , 815 F.2d at 688, 2 USPQ2d at 1278. The Board erred by concluding otherwise.

D. *Unexpected Results .*

Because we reverse for failure to establish a *prima facie* case of obviousness, we need not reach Fine's contention that the Board failed to accord proper weight to the objective evidence of unexpected superior results. *Id* .

E. *The "Flame" Claims .*

[4] Claims 62, 68, 69, 79, 85 and 86 relate to the oxygen-rich flame conversion means of the claimed invention. These "flame" claims depend from either apparatus claim 60 or method claim 77. Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co* ., 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987); *In re Abele* , 684 F.2d 902, 910, 214 USPQ 682, 689 (CCPA 1982); *see also In re Sernaker* , 702 F.2d 989, 991, 217 USPQ 1, 3 (Fed. Cir. 1983). In view of our conclusion that claims 60 and 77 are nonobvious, the dependent "flame" claims are also patentable.

Conclusion

The Board's decision affirming the Examiner's rejection of claims 60, 62, 63, 68, 69, 77, 79, 80, 85 and 86 of Fine's application as unpatentable over the prior art under 35 U.S.C. §103 is *REVERSED* .

Footnotes

Footnote *. The Solicitor argues that the contents of Attachment C of Fine's brief were not before the Board and may not properly be considered here. However, we need not

rely on Attachment C. It is merely illustrative of the qualitative separation of nitrogen compounds which occurs in Fine's system. The fact that the various constituents exit at discrete intervals is shown by the specification which was before the Board and which may appropriately be considered on appeal. *See, e.g., Astra-Sjuco, A.B. v. United States Int'l Trade Comm'n* , 629 F.2d 682, 686, 207 USPQ 1, 5 (CCPA 1980) (claims must be construed in light of specification).

Dissenting Opinion Text

Dissent By:

Smith, circuit judge, dissenting.

I respectfully dissent. I am of the firm belief that the prior art references, relied upon by the PTO to establish its prima facie case of obviousness, in combination teach and suggest Fine's invention to one skilled in the art. Also, I firmly believe that Fine failed to rebut the PTO's prima facie case. On this basis, I would affirm the board's determination sustaining the examiner's rejection, pursuant to 35 U.S.C. §103, of Fine's claims on appeal before this court.

- End of Case -

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W.L. Gore & Associates, Inc. v. Garlock, Inc.

(CA FC)
220 USPQ 303
Decided Nov. 14, 1983
Nos. 83-613/614
U.S. Court of Appeals Federal Circuit

Headnotes

PATENTS

1. Court of Appeals for the Federal Circuit -- Weight given decision reviewed (§ 26.59)

Parties' argument relating to salutory injunction of FRCivP 52(a) cannot be controlling on all issues, where dispositive legal error occurred in interpretation and application of patent statute, 35 USC.

2. Court of Appeals for the Federal Circuit -- Weight given decision reviewed (§ 26.59)

Findings that rest on erroneous view of law may be set aside on that basis.

3. Construction of specification and claims -- Claim defines invention (§ 22.30)

Claims measure and define invention.

4. Construction of specification and claims -- Combination claims (§ 22.35)

Infringement -- Process patents (§ 39.65)

Court's restriction of claimed multi-step process to one step constitutes error, whether done at behest of patentee relying on that restriction to establish infringement by one who employs only that one step in process otherwise distinct, or at behest of accused infringer relying on that restriction to establish invalidity by showing that one step in prior art

process otherwise distinct; invention must be considered as whole.

5. Court of Appeals for the Federal Circuit -- Weight given decision reviewed (§ 26.59)

CAFC is not at liberty to substitute its own for district court's findings underlying district court's conclusion that claim is invalid.

6. Patentability -- Anticipation -- Process (§ 51.225)

It is irrelevant that those using invention may not have appreciated results where patent owner's operation of device is consistent, reproducible use of claimed invention; were that alone enough to prevent anticipation, it would be possible to obtain patent for old and unchanged process.

7. Use and sale -- Extent and character of use (§ 69.5)

Nonsecret use of claimed process in usual course of producing articles for commercial purposes is public use.

8. Use and sale -- Extent and character of use (§ 69.5)

Patentees' commercialization of product produced by its patented process can result in forfeiture of patent granted them for that process on application filed by them more than one year later; however, third party secret commercialization of process cannot be bar to patent grant on that process.

9. Patent grant -- Intent of patent laws (§ 50.15)

Early public disclosure is linchpin of patent system.

10. Interference -- Priority (§ 41.70)

Law disfavors prior inventor who benefits from process by selling its product but suppresses, conceals, or otherwise keeps process from public, as against later inventor who promptly files patent application from which public will gain disclosure of process.

11. Patentability -- Evidence of -- In general (§ 51.451)

District court that in its consideration of prior art disregarded unpredictability and unique nature of product to which claimed inventions relate errs.

12. Construction of specification and claims -- By prior art (§ 22.20)

District court that in its consideration of prior art considers claims in less than their

entireties errs.

13. Patentability -- Evidence of -- Suggestions of prior art (§ 51.469)

District court that considers references in less than their entireties, i.e., in disregarding disclosures in references that diverge from and teach away from invention at hand, errs.

14. Construction of specification and claims -- Comparison with other claims (§ 22.40)

Claims must be considered individually and separately.

15. Patentability -- Anticipation -- Combining references (§ 51.205)

There must have been something present in teachings in references to suggest to one skilled in art that claimed invention before court would have been obvious.

16. Patentability -- Evidence of -- Suggestions of prior art (§ 51.469)

Fact that patentee proceeded contrary to accepted wisdom of prior art is strong evidence of nonobviousness.

17. Patentability -- Tests of -- Skill of art (§ 51.707)

Imbuing one of ordinary skill in art with knowledge of invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to insidious effect of hindsight syndrome wherein that which only inventor taught is used against its teacher.

18. Patentability -- Invention -- In general (§ 51.501)

Patentability -- Tests of -- Skill of art (§ 51.707)

Decisionmaker must forget what he or she has been taught at trial about claimed invention and cast mind back to time invention was made to occupy mind of one skilled in art who is presented only with references, and who is normally guided by then-accepted wisdom in art.

19. Pleading and practice in courts -- Burden of proof -- Validity (§ 53.138)

Presumption for patent grant -- Patent Office consideration of prior art (§ 55.5)

It is not law that presumption of validity is weakened greatly where Patent Office has failed to consider pertinent prior art; presumption has no separate evidentiary value; it cautions decisionmaker against rush to conclude invalidity; submission of additional art

that is merely "pertinent" does not dispel that caution; however, inescapable burden of persuasion on one who would prove invalidity remains throughout trial.

20. Pleading and practice in courts -- Burden of proof -- Validity (§ 53.138)

Presumption from patent grant -- Patent Office consideration of prior art (§ 55.5)

Burden of proving invalidity may be facilitated by prior art that is more pertinent than that considered by PTO.

21. Patentability -- Evidence of -- In general (§ 51.451)

District court that specifically declines to consider objective evidence of nonobviousness errs; that evidence can often serve as insurance against insidious attraction of siren hindsight when confronted with difficult task of evaluating prior art; even when prior art evidence points more in direction of nonobviousness than obviousness, objective evidence may tend to reassure decisionmaker.

22. Patentability -- Anticipation -- In general (§ 51.201)

Anticipation requires disclosure in single prior art reference of each element of claim under consideration.

23. Patentability -- Anticipation -- Process (§ 51.225)

Patentability -- Composition of matter (§ 51.30)

Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting characteristics of products that might result from practice of processes disclosed in references.

24. Patentability -- Anticipation -- Infringement as test (§ 51.211)

Accused infringer's employment of process of dominating patent is not anticipation of invention described and claimed in improvement patent.

25. Patentability -- Anticipation -- In general (§ 51.201)

Patentability -- Invention -- In general (§ 51.501)

Inherency and obviousness are distinct concepts.

26. Patentability -- Evidence of -- In general (§ 51.451)

All evidence bearing on obviousness issue, as with any other issue raised in conduct

of judicial process, must be considered and evaluated before required legal conclusion is reached.

27. Patentability -- Evidence of -- In general (§ 51.451)

Objective evidence of nonobviousness, i.e., "indicia" of Graham v. John Deere Co., 148 USPQ 459, may in given case be entitled to more weight or less, depending on its nature and its relationship to invention's merits; it may be most pertinent, probative, and revealing evidence available to aid in reaching conclusion on obvious/nonobvious issue.

28. Patentability -- Evidence of -- Commercial success -- In general (§ 51.4551)

Praise greeting products claimed in patent from suppliers, including owner of prior art patent, is objective evidence of nonobviousness.

29. Patentability -- Composition of matter (§ 51.30)

Claim to new product is not required to include critical limitations.

30. Specification -- Sufficiency of disclosure (§ 62.7)

Patents are written to enable those skilled in art to practice invention, not public, and Section 112 speaks as of application filing date, not as of time of trial.

31. Specification -- Sufficiency of disclosure (§ 62.7)

Section 112 requires that inventor set forth best mode of practicing invention known to him at time application was filed.

32. Claims -- Indefinite -- In general (§ 20.551)

Use of "stretching at rate exceeding specific percent per second" in claims is not indefinite.

33. Claims -- Specification must support (§ 20.85)

It is claimed invention for which enablement is required.

34. Specification -- Sufficiency of disclosure (§ 62.7)

Patent is not invalid merely because some experimentation is needed; patent is invalid only when those skilled in art are required to engage in undue experimentation to practice invention.

35. Construction of specification and claims -- Claim defines invention (§ 22.30)

Distinguishing what infringes from what does not is role of claims, not of specification.

36. Construction of specification and claims -- Defining terms (§ 22.45)

Patent applicant can be his own lexicographer.

37. Defenses -- Fraud (§ 30.05)

Fraud must be shown by clear and convincing evidence; state of mind of one making representations is most important of elements to be considered in determining existence of fraud; good faith and subjective intent, while they are to be considered, should not necessarily be made controlling; under ordinary circumstances, fact of misrepresentation coupled with proof that party making it had knowledge of its falsity is enough to warrant drawing inference that there was fraudulent intent; where public policy demands complete and accurate disclosure it may suffice to show nothing more than that misrepresentations were made in atmosphere of gross negligence as to their truth.

38. Pleading and practice in courts -- Issues determined -- Validity and infringement (§ 53.505)

Better practice is for district court to decide both validity and infringement issues when both are contested at trial, enabling conduct of single appeal and disposition of entire case in single appellate opinion.

39. Infringement -- Tests of -- Comparison with claim (§ 39.803)

Infringement is decided with respect to each asserted claim as separate entity.

Particular patents -- Porous Products

3,953,566, Gore, Process for Producing Porous Products, holding of invalidity of claims 3 and 19 reversed and of claims 1 and 17 affirmed.

4,187,390, Gore, Porous Products and Process Therefor, holding of invalidity reversed.

Case History and Disposition:

Appeal from District Court for the Northern District of Ohio, Manos, J.; 220 USPQ 220 .

Consolidated actions by W. L. Gore & Associates, Inc., against Garlock, Inc., for patent infringement, in which defendant counterclaims for declaratory judgment of patent invalidity, noninfringement, fraudulent solicitation, and entitlement to attorney fees. From judgment for defendant, plaintiff appeals and defendant cross-appeals. Affirmed in part, reversed in part, and remanded; Davis, Circuit Judge, concurring in result in part and dissenting in part, with opinion.

Attorneys:

David H. Pfeffer, New York, N.Y. (J. Robert Dailey and Janet Dore, both of New York, N.Y., and John S. Campbell, Newark, Del., of counsel) for appellant.

John J. Mackiewicz, Philadelphia, Pa. (Dale M. Heist, Philadelphia, Pa., on the brief, Bernard Ouziel, New York, N.Y., of counsel) for appellee.

Judge:

Before Markey, Chief Judge, and Davis and Miller, Circuit Judges.

Opinion Text

Opinion By:

Markey, Chief Judge.

Appeal from a judgment of the District Court for the Northern District of Ohio holding U.S. Patents 3,953,566 ('566) and 4,187,390 ('390) invalid. We affirm in part, reverse in part, and remand for a determination of the infringement issue.

Background

Tape of unsintered polytetrafluorethylene (PTFE) (known by the trademark TEFLON of E.I. du Pont de Nemours, Inc.) had been stretched in small increments. W. L. Gore & Associates, Inc. (Gore), assignee of the patents in suit, experienced a tape breakage problem in the operation of its "401" tape stretching machine. Dr. Robert Gore, Vice President of Gore, developed the invention disclosed and claimed in the '566 and '390 patents in the course of his effort to solve that problem. The 401 machine was disclosed and claimed in Gore's U.S. Patent 3,664,915 ('915) and was the invention of Wilbert L. Gore, Dr. Gore's father. PTFE tape had been sold as thread seal tape, i.e., tape used to keep pipe joints from leaking. The '915 patent, the application for which was filed on October 3, 1969, makes no reference to stretch rate, at 10% per second or otherwise, or to

matrix tensile strength in excess of 7,300 psi.

Dr. Gore experimented with heating and stretching of highly crystalline PTFE rods. Despite slow, careful stretching, the rods broke when stretched a relatively small amount. Conventional wisdom in the art taught that breakage could be avoided only by slowing the stretch rate or by decreasing the crystallinity. In late October 1969, Dr. Gore discovered, contrary to that teaching, that stretching the rods as fast as possible enabled him to stretch them to more than ten times their original length with no breakage. Further, though the rod was thus greatly lengthened, its diameter remained virtually unchanged throughout its length. The rapid stretching also transformed the hard, shiny rods into rods of a soft, flexible material.

Gore developed several PTFE products by rapidly stretching highly crystalline PTFE, including: (1) porous film for filters and laminates; (2) fabric laminates of PTFE film bonded to fabric to produce a remarkable material having the contradictory properties of impermeability to liquid water and permeability to water vapor, the material being used to make "breathable" rainwear and filters; (3) porous yarn for weaving and braiding into other products, like space suits and pump packing; (4) tubes used as replacements for human arteries and veins; and (5) insulation for high performance electric cables.

On May 21, 1970, Gore filed the patent application that resulted in the patents in suit. The '566 patent has 24 claims directed to processes for stretching highly crystalline, unsintered, PTFE. The processes, inter alia, include the steps of stretching PTFE at a rate above 10% per second and at a temperature between about 35°C and the crystalline melt point of PTFE. The '390 patent has 77 claims directed to various products obtained by processes of the '566 patent.

It is effectively undisputed that the present inventions filled a long sought yet unfilled need. The United States Army and the research director of a Garlock Inc. (Garlock) customer had been looking for and following up every remote lead to a waterproof/breathable material for many years.

It is undisputed that the present inventions enjoyed prompt and remarkable commercial success due to their merits and not to advertising or other extraneous causes.

It is undisputed that the inventions provide the most important synthetic material available for use in vascular surgery, hundreds of thousands of persons having received artificial arteries formed of the patented products since 1976, and that the patented products have unique properties useful in other medical procedures, in communications satellites, radar systems, and electrical applications.

It is undisputed that the major sources of PTFE, ICI and du Pont, greeted the patented products as "magical," 'bewitching," "a remarkable new material," and one that "differs from other processed forms of Teflon."

It is undisputed that the patented products were met with skepticism and disbelief by at least one scientist who had worked with PTFE at du Pont for many years and who testified as an expert at trial.

It is undisputed that Garlock first produced an accused product in response to a

customer's request for a substitute for the patented product, that Garlock advertised its accused product as a "new form" of PTFE and as "a versatile new material which provides new orders of performance for consumer, industrial, medical and electrical applications," and that the customer describes that accused product as "a new dimension in rainproof/breathable fabrics."

Proceedings

On Nov. 2, 1979, Gore sued Garlock for infringement of process claims 3 and 19 of the '566 patent, and sought injunctive relief, damages and attorney fees. Garlock counterclaimed on Dec. 18, 1979, for a declaratory judgment of patent invalidity, non-infringement, fraudulent solicitation, and entitlement to attorney fees. On Feb. 7, 1980, Gore filed a second suit for infringement of product claims 14, 18, 36, 43, 67 and 77 of the '390 patent. In light of a stipulation, the district court consolidated the two suits for trial.

Gore alleged infringement of certain claims by certain products:

Table set at this point is not available. See table in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

At trial, Garlock addressed only claims 1, 3, 17, and 19 of the '566 patent and claims 1, 9, 12, 14, 18, 35, 36, 43, 67 and 77 of the '390 patent. See Appendix to this opinion.

The district court, in a thorough memorandum accompanying its judgment, and in respect of the '566 patent: (1) found claim 1 anticipated under 35 U.S.C. §102(a) by Gore's use of its 401 machine and use by the Budd Company (Budd) of a Cropper machine; (2) declared all claims of the patent invalid under 102(b) because the invention had been in public use and on sale more than one year before Gore's patent application, as evidenced by Budd's use of the Cropper machine; (3) held claims 1, 3, 17 and 19 invalid for obviousness under 35 U.S.C. §103, on the basis of various reference pairings: (a) Japanese patent 13560/67 (Sumitomo) with U.S. patent 3,214,503 (Markwood); (b) U.S. patent 2,776,465 (Smith) with Markwood; or (c) Gore's '915 patent with Sumitomo; and (4) held all claims invalid as indefinite under 35 U.S.C. §112. [1]

In its opinion respecting the '390 patent, the district court held: (1) claims 1, 9, 12, 14, 18, 35, 36, 43, 67 and 77 invalid §§102 and 103 in view of Sumitomo and Smith; and (2) all claims invalid as indefinite under §112.

The court found that Gore did not commit fraud before the Patent and Trademark Office (PTO), denied Garlock's request for attorney fees, and refrained from deciding the infringement issue.

Issues

Did the district court err in: (1) its holding of invalidity under §§102(a), 102(b), 103 and 112; (2) its finding that Gore did not commit fraud on the PTO; or (3) denying attorney fees.

Opinion

This hard fought and bitterly contested case involved over two years of discovery, five weeks of trial, the testimony of 35 witnesses (19 live, 16 by deposition), and over 300 exhibits. The district court issued an exhaustive 37-page memorandum opinion reflective of a careful, conscientious approach to the determination of the many issues presented at trial.

The record on appeal consists of 2000 pages. The parties' briefs total 199 pages. In those briefs, counsel repeatedly accuse each other of numerous and serious breaches of the duty of candor owed the court. Each cites instances in which the testimony, the findings, and the record are or are said to be quoted in part and out of context. As a result, the usefulness and reliability of the briefs as means of informing the court has been greatly diminished if not destroyed, and careful, time-consuming study of all exhibits and each page of the record has been required.

Appellant cited 80 prior court opinions in its main brief. Appellee's brief totally ignores all but two of those citations, but adds 57 more. Appellant's reply brief cites 126 prior court opinions, 34 earlier cited, 67 newly cited, and 25 of those cited by appellee. Appellee's reply brief cites 17 prior court opinions, 4 earlier cited, 7 newly cited, and 6 of the 147 cited by appellant. Accordingly, 211 prior court opinions have been evaluated in relation to the proof found in the record.

In light of the entire record and the applicable law, we are convinced that Garlock failed to carry its burden of proving all claims of the present patents invalid.

Standard of Review

[1]

[2] Where, as here, dispositive legal error occurred in interpretation and application of the patent statute, 35 U.S.C., the parties' arguments relating to the salutory injunction of Fed.RuleCiv.P. 52(a) cannot be controlling on all issues. Findings that "rest on an erroneous view of the law may be set aside on that basis," Pullman-Standard v. Swint, 456 U.S. 273 (1982). Thus it is unnecessary here to set aside any probative fact found by the district court on the basis of its being clearly erroneous, or to engage in what would be an inappropriate reweighing of the facts.

Among the legal errors extant in the record, each of which is discussed below, are (1) the invention set forth in each claim was not in each instance considered as a whole; (2) 35 U.S.C. §102(b) was applied though criteria for its application were not present; (3) the references were not assessed in their entireties; (4) an inherency theory under §§102 and 103 was inappropriately applied; (5) that which only the inventor taught was attributed to the prior art; (6) individual steps in prior art processes dealing with materials distinct from those with which the present inventions dealt were erroneously equated to steps in the claimed processes; (7) objective evidence of nonobviousness was disregarded; and (8) the function and application of §112 were misconstrued.

Because it permeated so much of the district court's analysis, we note more fully its frequent restriction of its consideration to 10% per second rate of stretching, which it called the "thrust of the invention." That approach is repeated throughout Garlock's briefs, which refer repeatedly to the "thrust of the invention," to "the inventive concept," and to the claims "shorn of their extraneous limitations." That facile focusing on the "thrust," "concept," and "shorn" claims, resulted in treating the claims at many points as though they read differently from those actually allowed and in suit.

[3] It is true that Dr. Gore emphasized rapid stretching, for example, as well as the amount of stretch and other process limitations, during prosecution of the application for the '566 patent. Yet it is the claims that measure and define the invention. Aro Manufacturing Co. v. Convertible Top Replacement Co., 365 U.S. 336, 339, 128 USPQ 354 (1961); Bowser, Inc. v. U.S., 388 F.2d 346, 349, 156 USPQ 406, 409 (Ct. Cl. 1967).

[4] Each claimed invention must be considered as a whole. 35 U.S.C. §103; Schenck, A.G. v. Nortron Corp., 218 USPQ 698, 700 (Fed. Cir. 1983). In determining obviousness, there is "no legally recognizable or protected 'essential,' 'gist,' or 'heart' of the invention." Aro, 365 U.S. at 345. A court's restriction of a claimed multi-step process to one step constitutes error, whether done at the behest of a patentee relying on that restriction to establish infringement by one who employs only that one step in a process otherwise distinct, or at the behest of an accused infringer relying on that restriction to establish invalidity by showing that one step in a prior art process otherwise distinct.

(1) Invalidity
(a) '566 Patent
(i) §102(a) and The 401 Machine

It is undisputed that the district court held only claim 1 of the '566 patent to have been anticipated under §102(a) by operation of the 401 machine in the Gore shop before Dr. Gore's invention in late October 1969. It did so on the deposition testimony of two former Gore employees, documents, and drawings of the 401 machine.

In August 1969, Gore offered to sell to Export Tool Company (Export) tape "to be made" on the 401 machine. Tape made on the 401 machine was shipped to Export on October 24, 1969. The trial judge found the rolls on the 401 machine were, at least at some point in time before October 1969, spaced less than four feet apart and that the rate of stretch accomplished in operating that machine (admittedly operated in accord with the description of machine operation in the '915 patent) must have been greater than 10% per second. The district court credited testimony that Teflon 6-c, a highly crystalline form of Teflon, was used because it was the standard resin at the time, and that the tape was stretched at a temperature above 35°C. Thus it cannot be said that the record fails to support the district court's finding that the limitations of claim 1 were met by Gore's operation of the 401 machine before Dr. Gore's asserted "late October 1969" date of invention. Though he was working with the operation of the 401 machine, Dr. Gore offered no proof that his invention date was before the date of shipment to Export.

[5] Gore, seeking a review here of the evidence, points to certain inadequacies as indicating a failure to meet the required clear and convincing standard under §102(a). At the time of trial, the district court, bound by precedent then applicable, applied a preponderance of the evidence test. Gord asserts, erroneously, that the clearly erroneous standard does not therefore apply on this appeal. Gore does not, however, point to any basis on which the district court's findings must be held to have been clearly erroneous under the clear and convincing standard. We are not at liberty, of course, to substitute

our own for the district court's findings underlying its conclusion that claim 1 is invalid.

[6] Gore's operation of the 401 machine must thus be viewed as a consistent, reproducible use of Dr. Gore's invention as set forth in claim 1, and it is therefore irrelevant that those using the invention may not have appreciated the results. General Electric Co. v. Jewel Incandescent Lamp Co., 326 U.S. 242, 248, 67 USPQ 155, 157-58 (1945). Were that alone enough to prevent anticipation, it would be possible to obtain a patent for an old and unchanged process. Ansonia Brass & Copper Co. v. Electric Supply Co., 144 U.S. 11, 18 (1892); see, H.K. Regar & Sons, Inc. v. Scott & Williams, Inc., 63 F.2d 229, 231, 17 USPQ 81, 83 (2d Cir. 1933).

[7] The nonsecret use of a claimed process in the usual course of producing articles for commercial purposes is a public use. Electric Storage Battery Co. v. Shimadzu, 307 U.S. 5, 20, 41 USPQ 155, 161 (1939), and there was no evidence that any different process was used to produce the articles shipped to Export.

Thus it cannot be said that the district court erred in determining that the invention set forth in claim 1 of '566 patent was known or used by others under §102(a), as evidenced by Gore's operation of the 401 machine before Dr. Gore's asserted date of that invention.

In view of our affirmance of the judgment reached on claim 1 under 102(a), we need not discuss other asserted grounds of invalidity of claim 1. There was, however, no evidence whatever that the inventions set forth in other claims, of either the '566 or the '390 patent, were known or used by others as a result of Gore's operation of the 401 machine before late October 1969.

(ii) §102(b) and the Cropper Machine

In 1966 John W. Cropper (Cropper) of New Zealand developed and constructed a machine for producing stretched and unstretched PTFE thread seal tape. In 1967, Cropper sent a letter to a company in Massachusetts, offering to sell his machine, describing its operation, and enclosing a photo. Nothing came of that letter. There is no evidence and no finding that the present inventions thereby became known or used in this country.

In 1968, Cropper sold his machine to Budd, which at some point thereafter used it to produce and sell PTFE thread seal tape. The sales agreement between Cropper and Budd provided:

> **ARTICLE "E" - PROTECTION OF TRADE SECRETS Etc.**
>
> *1. BUDD* agrees that while this agreement is in force it will not reproduce any copies of the said apparatus without the express written permission of Cropper nor will it divulge to any person or persons other than its own employees or employees of its affiliated corporations any of the said known-how or any details whatsoever relating to the apparatus.
>
> *2. BUDD* agrees to take all proper steps to ensure that its employees observe the terms of Article "E" 1 and further agrees that whenever it is proper to do so it will take legal action in a Court of competent jurisdiction to enforce any one or more of the legal or equitable remedies available to a trade secret plaintiff.

Budd told its employees the Cropper machine was confidential and required them to sign confidentiality agreements. Budd otherwise treated the Cropper machine like its other manufacturing equipment.

A former Budd employee said Budd made no effort to keep the secret. That Budd did not keep the machine hidden from employees legally bound to keep their knowledge confidential does not evidence a failure to maintain the secret. Similarly, that du Pont employees were shown the machine to see if they could help increase its speed does not itself establish a breach of the secrecy agreement. There is no evidence of when that viewing occurred. There is no evidence that a viewer of the machine could thereby learn anything of which process, among all possible processes, the machine is being used to practice. As Cropper testified, looking at the machine in operation does not reveal whether it is stretching, and if so, at what speed. Nor does looking disclose whether the crystallinity and temperature elements of the invention set forth in the claims are involved. There is no evidence that Budd's secret use of the Cropper machine made knowledge of the claimed process accessible to the public.

The district court held all claims of the '566 patent invalid under 102(b), supra, note 3, because "the invention" was "in public use [and] on sale" by Budd more than one year before Gore's application for patent. Beyond a failure to consider each of the claims independently, 35 U.S.C. §282; Altoona Publix Theatres, Inc. v. American Tri-Ergon Corp., 294 U.S. 477, 487, 24 USPQ 308 (1935), and a failure of proof that the claimed inventions as a whole were practiced by Budd before the critical May 21, 1969 date, it was error to hold that Budd's activity with the Cropper machine, as above indicated, was a "public" use of the processes claimed in the '566 patent, that activity having been secret, not public.

Assuming, arguendo, that Budd sold tape produced on the Cropper machine before October 1969, and that that tape was made by a process set forth in a claim of the '566 patent, the issue under §102(b) is whether that sale would defeat Dr. Gore's right to a patent on the process inventions set forth in the claims.

[8] If Budd offered and sold anything, it was only tape, not whatever process was used in producing it. Neither party contends, and there was no evidence, that the public could learn the claimed process by examining the tape. If Budd and Cropper commercialized the tape, that could result in a forfeiture of a patent granted them for their process on an application filed by them more than a year later. D.L. Auld Co. v. Chroma Graphics Corp., No. 83-585, slip op. at 5-6 (Fed. Cir. Aug. 15, 1983); See Metalizing Engineering Co. v. Kenyon Bearing & Auto Parts Co., 153 F.2d 516, 68 USPQ 54 (2d Cir. 1946). There is no reason or statutory basis, however, on which Budd's and Cropper's secret commercialization of a process, if established, could be held a bar to the grant of a patent to Gore on that process.

[9]

[10] Early public disclosure is a linchpin of the patent system. As between a prior inventor who benefits from a process by selling its product but suppresses, conceals, or otherwise keeps the process from the public, and a later inventor who promptly files a patent application from which the public will gain a disclosure of the process, the law favors the latter. See Horwath v. Lee, 564 F.2d 948, 195 USPQ 701 (CCPA 1977). The district court therefore erred as a matter of law in applying the statute and in its

determination that Budd's secret use of the Cropper machine and sale of tape rendered all process

claims of the '566 patent invalid under §102(b).

(iii) §103

In considering claims 1, 3, 17, and 19 of the '566 patent, the district court recognized that analysis of the obviousness issue under §103 requires determination of the scope and content of the prior art, the differences between the prior art, and the claims at issue, and the level of ordinary skill in the pertinent art. Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

[11]

[12]

[13] In its consideration of the prior art, however, the district court erred in not taking into account the import of the markedly different behavior of PTFE from that of conventional thermoplastic polymers clearly established and undisputed on the record, and in thus disregarding the unpredictability and unique nature of the unsintered PTFE to which the claimed inventions relate, In re Whiton, 420 F.2d 1082, 164 USPQ 455 (CCPA 1970); in considering claims in less than their entireties, Schenck, supra; and in considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand. In re Kuderna, 426 F.2d 385, 165 USPQ 575 (CCPA 1970).

Invalidity of claim 1 under §102(a) having been determined, it is unnecessary to discuss in detail the applicability of §103 to that claim. If claim 1 had not been held anticipated under §102(a) in light of operation of the 401 machine, it is clear from the discussion here that claim 1 could not properly have been held invalid under §103.

Claim 3 depends from and thus incorporates claim 1 but specifies a rate of stretch of 100% per second. Claim 17 also depends from claim 1 and specifies an amount of stretch of about twice the original length. Claim 19 depends from claim 17 but specifies an amount of stretch of about five times the original length.

U.S. patent 2,983,961 to Titterton, Volume 13 of the Encyclopedia of Polymer Science and Technology (1970), the Sumitomo patent, and witnesses for both parties, establish that teachings related to conventional thermoplastic polymers are inapplicable to PTFE.

Articles by Dogliotti and Yelland, Effect of Strain Rate on the Viscoelastic Properties of High Polymeric Fibrous Materials, 4 High Speed Testing 211 (1964) and Robinson and Graham, Methods of Characterization of Polymeric Materials by High Speed Testing Techniques, 5 High Speed Testing 261 (1965), teach that conventional plastics and sintered PTFE can be stretched further if stretched slowly. Dr. Gore demonstrated at trial and at oral argument before us that an attempt to stretch highly crystalline, unsintered PTFE slowly results in breakage, and that rapid stretching produces a greatly lengthened rod of soft, flexible material.

The '566 patent contains an example of stretching an article to 16 times its length. Smith and the '915 patent teach that PTFE could not be stretched beyond four times its

length without heating it to above its crystalline melt temperature, a step avoided by Dr. Gore and as set forth in the claims.

Sumitomo teaches that there is a length limit to stretching unsintered PTFE, and does not suggest what that limit might be. Markwood, U.S. patent 3,208,100 to Nash (Nash), and U.S. patent 2,823,421 to Scarlett (Scarlett) teach that *non-PTFE* thermoplastics can be stretched rapidly and to extended lengths, and *also* teach reduction, elimination, or avoidance of crystallinity before stretching.

The disclosure in the Smith and '915 patents that a PTFE article may be stretched to as much as four times its length encompasses the step of stretching to twice its length set forth in claim 17 and establishes that such step would have been obvious.

[14] Claims 3 and 19 must be considered individually and separately. 35 U.S.C. §282. Nowhere, in any of the references, is it taught or suggested that highly crystalline, unsintered PTFE could be stretched at a rate of about 100% per second as required by asserted claim 3. Nor is it anywhere suggested that by rapid stretching a PTFE article be stretched to more than five times its original length as required by asserted claim 19. On the contrary, the art as a whole teaches the other way.

[15] In concluding that obviousness was established by the teachings in various pairs of references, the district court lost sight of the principle that there must have been something present in those teachings to suggest to one skilled in the art that the claimed invention before the court would have been obvious. In re Bergel, 292 F.2d 955, 956-57, 130 USPQ 206, 208 (CCPA 1961); In re Sponnoble, 405 F.2d 578, 585, 160 USPQ 237, 244 (CCPA 1969).

The court's pairing of Sumitomo and Markwood disregarded, as above indicated, the undisputed evidence that the unsintered PTFE of Sumitomo does not respond to the conventional plastics processing of Markwood and the art recognition of that fact. Whiton, supra, 420 F.2d at 1085, 164 USPQ at 457.

In evaluating claim 19, for example, the pairing disregarded Sumitomo's limited

length of stretch teaching. In evaluating claim 3, the court recognized that Sumitomo made no mention of rate of stretch. Looking to Markwood to supply that teaching disregarded not only the conventional plastics-unsintered PTFE distinction but also the clear divergence of Markwood's teaching that crystallinity must be reduced or avoided from the presence of "highly crystalline" in all claims of the '566 patent.

Similarly, and for many of the same reasons, the pairing of Markwood's and Smith's teachings was an inappropriate basis for concluding that the processes set forth in claims 3 and 19 would have been obvious. As above indicated, Markwood's rapid stretching of conventional plastic polypropylene with reduced crystallinity would not suggest rapid stretching of highly crystalline PTFE, in light of teachings in the art that PTFE should be stretched slowly. The Smith patent is owned by du Pont, where Dr. Gore's process invention was considered to have produced a "remarkable new material." That circumstance is not surprising, for Smith, though dealing with PTFE, says not a word about any rate of stretch.

Lastly, the pairing of Sumitomo and the '915 patent suffers from the same

shortcomings. The pairing resulted from a hypothetical set forth in Garlock's post trial brief, and was based on no testimony or other evidence in the record. In respect to claim 3, neither reference mentions rate of stretch or suggests its importance. In respect of claim 19 both references point away from the claimed invention in their limited length-of-stretch teachings. The '915 patent states: "the 65 percent expanded material could be expanded a second time for an additional 65 percent expansion or a total length increase ratio of 1:2.72 [less than three times the original length). However, great care was necessary to obtain a uniformly expanded material at these very great expansion ratios." Thus the '915 patent suggests that the amount of stretch of 500% set forth in claim 19 (more than five times the original length) is not possible.

As indicated, Sumitomo and Smith are totally silent respecting the rate of stretch, and there is simply no teaching in the art that would suggest to one of ordinary skill that Markwood's fast stretching of other thermoplastics could or should be employed in the process of treating PTFE taught by either Sumitomo or Smith. Indeed, Smith not only says nothing about rate of stretch, its preferred teaching is away from other elements of the inventions set forth in claims 3 and 19 Smith discloses that stretching should be done after the PTFE is heated above its crystalline melting point and with decreased crystallinity. Smith teaches:

> Below about 300°C it is *not possible* to draw more than about 4X [times] and while such draw ratios can be attained around 300°C and below the polymer's crystalline melting point with resultant orientation and improved properties it is preferred to use temperatures at or above the polymer's crystalline melting point. (Emphasis added).

Nash teaches that the film should be plasticized, i.e., made more viscous, before stretching. Contrary to that teaching, Dr. Gore did not reduce crystallinity before increasing the rate of stretch, but maintained the unsintered PTFE "highly crystalline" while stretching at a 100% per second rate and to more than five times, as set forth respectively in claims 3 and 19.

[16] On the entire record and in view of all the references, each in its entirety, it is clear that a person of ordinary skill confronted with a PTFE tape breakage problem would have either slowed the rate of stretching or increased the temperature to decrease the crystallinity. Dr. Gore did neither. He proceeded contrary to the accepted wisdom of the prior art by dramatically increasing the rate and length of stretch *and* retaining crystallinity. That fact is strong evidence of nonobviousness. United States v. Adams, 383 U.S. 39 (1966).

Having learned the details of Dr. Gore's invention, the district court found it within the skill of the art to stretch other material rapidly (Markwood); to stretch PTFE to increase porosity (Sumitomo); and to stretch at high temperatures (Smith). The result is that the claims were used as a frame, and individual, naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention. At no point did the district court, nor does Garlock, explain why that mosaic would have been obvious to one skilled in the art in 1969, or what there was in the prior art that would have caused those skilled in the art to disregard the teachings there found against making just such a mosaic. On the contrary, the references and the uncontested testimony, as above indicated, established that PTFE is sui generis. It is not surprising,

therefore, that, unlike the situation in Stratoflex, Inc. v. Aeroquip Corp., 218 USPQ 871 (Fed. Cir. 1983), there was no testimony and no finding that one skilled in the art would transfer conventional thermoplastic processes to those for unsintered PTFE, or would have been able to predict what would happen if they did.

[17] To imbue one of ordinary skill in the art with knowledge of the invention in suit,

when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

[18] It is difficult but necessary that the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art. Had that been here done the inventions set forth in the claims 3 and 19 of the '566 patent could only have been held non-obvious to those skilled in the art at the time those claimed inventions were made.

[19] Error in visualizing the burden of proof on obviousness may have contributed to the court's application here of the prior art. Adopting the phrase from earlier precedents, the court said "the presumption [of validity] is weakened greatly where the Patent Office has failed to consider pertinent prior art." That is not the law of established precedent in this court. SSIH Equipment S.A. v. ITC, 218 USPQ 678, 687 (Fed. Cir. 1983); Solder Removal Co. v. ITC, 582 F.2d 628, 633, 199 USPQ 129, 133, n. 9 (CCPA 1978). The presumption has no separate evidentiary value. It cautions the decisionmaker against a rush to conclude invalidity. Submission of additional art that is merely "pertinent" does not dispel that caution. It is difficult to imagine a patent law suit in which an accused infringer is unable to add some new "pertinent" art. The inescapable burden of persuasion on one who would prove invalidity, however, remains throughout the trial. 35 U.S.C. §282.

[20] The burden of proving invalidity may of course be facilitated by prior art that is *more pertinent* than that considered by the PTO. That did not happen here. In the present case, Sumitomo, Smith, and the '915 patent were among references considered by the PTO. Other references referred to as not considered were merely cumulative, disclosing nothing not disclosed in references that were considered by the PTO. The Canadian counterpart of Nash was considered by the PTO. The relevant disclosures of Markwood appear in Sandiford patent 3,544,671 and Paratheon patent 3,637,906, both considered by the PTO. The Russian Author's Certificate 240,997, assuming its status as prior art and whatever the material with which it dealt, contributed nothing beyond the teachings of the '915 patent considered by the PTO.

[21] As discussed more fully below, the district court erred in specifically declining to consider the objective evidence of nonobviousness. In re Sernaker, 702 F.2d 989, 996, 217 USPQ 1, 7 (Fed. Cir. 1983). That evidence can often serve as insurance against the insidious attraction of the siren hindsight when confronted with a difficult task of evaluating the prior art. Though the prior art evidence here pointed more in the direction

of nonobviousness than obviousness, the objective evidence may tend, as it did in Sernaker, supra, to reassure the decisionmaker.

In sum, the district court erred as a matter of law on this record in concluding that Garlock had met its burden of proving that the inventions of claims 3 and 19 of the '566 patent would have been obvious.

(b) ' *390 patent*

(i) *§102*

The district court found product claims 1, 9, 12, 14, 18 and 43 inherently anticipated because it found that the microstructure of nodes interconnected by fibrils is an inherent characteristic of paste-extruded PTFE products resulting from the process disclosed in Smith. The court found the first four of those claims and claim 43, plus claims 35, 36, 67 and 77 inherently anticipated because high strength PTFE products are inherent in the examples of Sumitomo.

The teachings of Smith include neither a disclosure nor a suggestion of "porous" products having a "microstructure characterized by nodes interconnected by fibrils" as required by the claims found to have been anticipated by Smith.

The teachings of Sumitomo do not include a disclosure of products having "a matrix tensile strength * * * above about 7,300 psi" as required by the claims found to have been anticipated by Sumitomo.

[22] Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. Soundscriber Corp. v. U.S., 360 F.2d 954, 960, 148 USPQ 298, 301, adopted, 149 USPQ 640 (Ct. Cl. 1966). Neither Smith nor Sumitomo disclose an invention set forth in any claim of the '390 patent.

The incongruity in findings that the different processes of Smith and Sumitomo each inherently produced identical products is striking.

Garlock attempted with expert testimony to overcome the prior art shortcomings as proof of anticipation. Gore rebutted with its own expert testimony. It is unnecessary, however, to resolve apparent conflicts in the divergent testimony, much if not all of which took

the form of pure unsupported assertion. No inter partes tests in which the Smith and Sumitomo processes were conducted are of record. No products of those processes were placed in evidence, and there was, of course, no analysis of any such evidentiary products.

Nor is it necessary to evaluate the inappropriate disparagement in Garlock's brief of Dr. Sperati as a "friend" of Gore.

[23] Given the unique nature of unsintered PTFE, we are not persuaded that the "effect" of the processes disclosed in Smith and Sumitomo, an "effect" undisclosed in those patents, would be always to inherently produce or be seen always to produce products meeting all of the claim limitations. Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references. In re Felton, 484 F.2d 495, 500, 179 USPQ 295, 298 (CCPA 1973). It is clear that the

teachings of neither Smith nor Sumitomo place the products claimed in the '390 patent in possession of the public.

The teachings of Smith and Sumitomo are so unacceptably vague concerning characteristics of products produced by their respective processes as not to support an anticipation rejection. That fact is confirmed by the PTO's having fully considered those references and by its having issued the '390 patent over them.

[24] Garlock's assertion that it employs a process covered by the Smith patent, if true, is irrelevant. The '390 patent was allowed over Smith as a reference. Assuming Smith is a dominating patent, the rule of law is clear that an accused infringer's employment of the process of a dominating patent does not render that employment an anticipation of an invention described and claimed in an improvement patent. As indicated, there is no present record basis for finding that the Smith process in itself necessarily and inherently results in the products, each considered in its entirety, in the claims of the '390 patent. The testimony of Garlock's expert about ex parte tests, the records of which he destroyed before trial, cannot serve as such a basis. The effusive praise of Dr. Gore's claimed products by the owner of the Smith patented process would appear, on the contrary, to confirm the action of the PTO in issuing the '390 patent.

Garlock has not met its burden of showing that claims 1, 9, 12, 14, 18, and 43 are anticipated by Smith or that claims 1, 9, 12, 14, 35, 36, 43, 67, and 77 are anticipated by Sumitomo.

(ii) *§103*

[25] The scope and content of the prior art and level of ordinary skill, discussed above in relation to the '566 patent, would be the same for the '390 patent. The district court did not, however, nor does Garlock, apply the Graham criteria, supra, to the '390 claims, apparently assuming that the claimed products, having been found inherent in the processes of Sumitomo and Smith, would have been obvious in view of those references. If so, that was error. Inherency and obviousness are distinct concepts. In re Spormann, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

In discussing inherency the district court did recognize differences between Smith's disclosure and the inventions set forth in claims 1, 9, 12, 14, 18, and 43, i.e., the absence from Smith of a description of the products of Smith's process as porous and the absence from Smith of a disclosure that those products have a microstructure characterized by nodes interconnected by fibrils.

Similarly, a difference between Sumitomo's disclosure and the inventions set forth in claims 1, 9, 12, 14, 35, 36, 43, 67, and 77 was recognized in the absence from Sumitomo of a quantification of the matrix tensile strengths of the products of Sumitomo's process. The district court also discussed differences between the dependent claims and the prior art. Because we conclude that the independent claims of the '390 patent are patentable over the art of record, we need not discuss the dependent claims.

[26] Having determined that the invention would have been obvious in view of the process of either Smith or Sumitomo, the district court did not discuss the strong showing of objective evidence of nonobviousness here present, saying with respect to one part of such evidence, "no amount of commercial success can save it." That approach was error. All evidence bearing on the issue of obviousness, as with any other issue raised in the conduct of the judicial process, must be considered and evaluated *before* the required

legal conclusion is reached. Stratoflex, supra, 218 USPQ at 879.

[27] The objective evidence of nonobviousness, i.e., the "indicia" of Graham, supra, may in a given case be entitled to more weight or less, depending on its nature and its relationship to the merits of the invention. It may be the most pertinent, probative, and revealing evidence available to aid in reaching a conclusion on the obvious/nonobvious issue. It should when present always be considered as an integral part of the analysis.

Gore's fabric laminates, for example, as set forth in claims 36 and 77, satisfied a long-felt

need for a material having the contradictory properties of being simultaneously breathable (allowing water vapor or perspiration to pass) and waterproof. The record establishes that such a material had long been sought by makers of rainwear and outerwear, and by the U.S. Army as well. That Gore's fabric laminates filled that need is attested by the rise in their annual dollar sales from zero to seven million in the first five years of their availability.

Gore's PTFE tubes for replacement of human arteries and veins, also satisfied a long-felt need. The uncontradicted evidence establishes that Gore's PTFE tubes hold blood without leaking, need not be pre-clotted with the patient's blood, are chemically inert, and, being breathable, are less likely to cause an air embolism. The value and uniqueness of those four properties make Gore's PTFE tubes, as described in unchallenged testimony, "the most important synthetic material presently existing" in vascular surgery, and, along with other evidence in the record, reflect the intended working of the patent system.

As discussed above, current annual sales of over sixty million dollars are attributable to the merits of the products claimed in the '390 patent. Considering the long-felt need for those products and the obvious commercial advantage to be gained by meeting that need, it is reasonable to conclude that the claimed products of the '390 patent would not have been obvious to persons of ordinary skill in the art at the time the claimed inventions were made.

[28] As above indicated, the praise which greeted the products claimed in the '390 patent from PTFE suppliers, including the owner of the Smith patent, is further objective evidence of nonobviousness.

[29] Garlock's appeal argument that the '390 claims are invalid because the recited minimum matrix tensile strengths are not "critical" is without merit. A claim to a new product is not legally required to include critical limitations. In re Miller, 441 F.2d 689, 696, 169 USPQ 597, 602 (CCPA 1971). The '390 claims are not drawn to optimization of ingredients or ranges within broad prior art teachings, but to new porous PTFE products of particular characteristics.

In sum, and in view of the difficulty of working with unsintered PTFE and its unpredictable response to various processing techniques, the vagueness of Smith and Sumitomo concerning the products produced by those processes, the filling of at least two long-felt needs and the commercial success described above, we conclude that the inventions set forth in claims 1, 9, 12, 14, 18, 35, 36, 43, 67, and 77 of the '390 patent

would not have been obvious to those skilled in the art at the time those inventions were made.

(c) §112 and the '566 and '390 patents

The patents in suit resulted from a single application and thus have substantially identical specifications. The holding of invalidity on the basis of §112 is common to both patents.

The district court found that the patents did not disclose sufficient information to enable a person of ordinary skill in the art to make and use the invention, as required by §112, first paragraph, and that certain claim language was indefinite, presumably in light of §112, second paragraph, because: (1) there was no definition in the specification of "stretch rate," different formulae for computing stretch rate having been developed and presented at trial; (2) there was no way taught in the specification to calculate the minimum rate of stretch above 35°C; (3) the phrase "matrix tensile strength" is indefinite; and (4) the phrase "specific gravity of the solid polymer" is indefinite.

[30] The findings rest on a misinterpretation of §112, its function and purpose. The district court considered whether certain terms would have been enabling to the public and looked to formula developments and publications occurring well after Dr. Gore's filing date in reaching its conclusions under §112. Patents, however, are written to enable those skilled in the art to practice the invention, not the public. In re Storrs, 245 F.2d 474, 478, 114 USPQ 293, 296-97 (CCPA 1957), and §112 speaks as of the application filing date, not as of the time of trial. In re Mott, 539 F.2d 1291, 1296, 190 USPQ 536, 541 (CCPA 1976). There was no evidence and no finding that those skilled in the art would have found the specification non-enabling or the claim language indefinite on May 21, 1970, when the application which resulted in issuance of Dr. Gore's patents was filed. Indeed, the expert quoted by the district court and whose testimony was primarily relied upon respecting formulae, was still in school at that time.

There is uncontradicted evidence in the record that at the time the application was filed "stretch rate" meant to those skilled in the art the percent of stretch divided by the time of stretching, and that the latter was measurable, for example, with a stopwatch. Concern for the absence from the specification of a formula for calculating stretch rate is therefore misplaced, and the post-filing date development of varying formulae, including Dr. Gore's later addition of a formula in his corresponding Japanese patent, is irrelevant.

[31] Section 112 requires that the inventor set forth the best mode of practicing the invention known to him at the time the application was filed. Calculating stretch rate at that time was accomplished by actually measuring the time required to stretch the PTFE material. That was the only mode then used by the inventor, and it worked. The record establishes that calculation by that mode would have been employed by those of ordinary skill in the art at the time the application was filed. As indicated, Dr. Gore's disclosure must be examined for §112 compliance in light of knowledge extant in the art on his application filing date.

[32] The district court, though discussing enablement, spoke also of indefiniteness of

"stretch rate," a matter having to do with §112, second paragraph, and relevant in assessment of infringement. The use of "stretching * * * at a rate exceeding about 10% per second" in the claims is not indefinite. Infringement is clearly assessable through use of a stopwatch. No witness said that could not be done. As above indicated, subsequently developed and therefore irrelevant formulae cannot be used to render non-enabling or indefinite that which was enabling and definite at the time the application was filed.

[33] Similarly, absence from the specification of a method for calculating the minimum rate of stretch above 35°C does not render the specification non-enabling. The specification discloses that "[t]he lower limit of expansion rates interact with temperature in a roughly logarithmic fashion, being much higher at higher temperatures." Calculation of minimum stretch rate above 35°C is nowhere in the claims, and it is the *claimed* invention for which enablement is required. The claims require stretching at a rate greater than 10% per second at temperatures between 35°C and the crystalline melt point of unsintered PTFE. That the minimum rate of stretch may increase with temperature does not render non-enabling Dr. Gore's specification, particularly in the absence of convincing evidence that those skilled in the art would have found it non-enabling at the time the application was filed.

[34] The district court invalidated both patents for indefiniteness because of its view that some "trial and error" would be needed to determine the "lower limits" of stretch rate above 10% per second at various temperatures above 35°C. That was error. Assuming some experimentation were needed, a patent is not invalid because of a need for experimentation. Minerals Separation, Ltd. v. Hyde, 242 U.S. 261, 270-71 (1916). A patent is invalid only when those skilled in the art are required to engage in *undue* experimentation to practice the invention. In re Angstadt, 537 F.2d 498, 503-04, 190 USPQ 214, 218 (CCPA 1976). There was no evidence and the court made no finding that undue experimentation was required.

[35] Moreover, the finding here rested on confusion of the role of the specification with that of the claims. The court found that the specification's failure to state the lower limit of stretch rate (albeit above 10% per second) at each degree of temperature above 35°C (a requirement for at least hundreds of entries in the specification) did not "distinguish processes performed above the 'lower limit' from those performed below the 'lower limit'." The claims of the '390 patent say nothing of processes and lower limits. Distinguishing what infringes from what doesn't is the role of the claims, not of the specification. It is clear that the specification is enabling, In re Storrs, supra, and that the claims of both patents are precise within the requirements of the law. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).

[36] The finding that "matrix tensile strength" is indefinite, like the other findings under §112, appears to rest on a confusion concerning the roles of the claims and the specification. While finding "matrix tensile strength" in the claims indefinite, the district court at the same time recognized that the specification itself disclosed how to compute matrix tensile strength, in stating "to compute matrix tensile strength of a porous specimen, one divides the maximum force required to break the sample by the cross sectional area of the porous sample, and then multiplies this quantity by the ratio of the specific gravity of the solid polymer divided by the specific gravity of the porous

specimen." Further, the specification provided the actual matrix tensile strength in several examples. It is well settled that a patent applicant may be his own lexicographer. In light of the disclosure of its calculation in the specification, we cannot agree that "matrix tensile strength" is either indefinite or non-enabling.

Nor does absence from the specification of a definition for "specific gravity of the solid polymer," a part of the computation of matrix tensile strength, render that computation indefinite. It is undisputed that in the many examples in the application the specific gravity values used for unsintered and sintered PTFE were 2.3 and 2.2, respectively. There was no testimony that those values were not known to persons of ordinary skill in the art or could not be calculated or measured. There is simply no support for the conclusion that "specific gravity of the solid polymer" is indefinite or that absence of its definition ren

ders the specification non-enabling. See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

We conclude that Garlock has failed to prove that at the time the application was filed, the specification was not enabling or that the claims were indefinite within the meaning of §112.

(2) Fraud

[37] Fraud must be shown by clear and convincing evidence. Norton v. Curtiss, 433 F.2d 779, 797, 167 USPQ 532, 546-47 (CCPA 1970).

> The state of mind of the one making the representations is probably the most important of the elements to be considered in determining the existence of "fraud." * * * Good faith and subjective intent, while they are to be considered, should not *necessarily* be made controlling. Under ordinary circumstances, the *fact* of misrepresentation coupled with proof that the party making it had knowledge of its falsity is enough to warrant drawing the inference that there was a fraudulent intent. Where public policy demands a complete and accurate disclosure it may suffice to show nothing more than that the misrepresentations were made in an atmosphere of gross negligence as to their truth. [emphasis in original].

Norton, 433 F.2d at 795-96; 167 USPQ at 545; see, Miller, Fraud on the PTO, 58 JPOS 271 (1976).

Garlock alleges fraud in Gore's representations that stretching PTFE tape at a rate greater than 10% per second was novel and that it produces a physical phenomenon. The district court found the evidence insufficient to establish that Gore had a specific intent to defraud the PTO. No basis exists for our overturning that finding. Accordingly, we agree with the district court that Garlock has failed to sustain its heavy burden of proving, by clear and convincing evidence, sufficient facts from which fraudulent intent can be inferred.

Garlock points to a September 4, 1975, Gore affidavit filed in the PTO that stated:

> 2. Prior to my invention disclosed in the captioned patent application, during production of expanded PTFE products by W. L. Gore & Associates, Inc.,

> the rate of stretching was neither measured nor controlled and to my knowledge did *not* involve stretching of unsintered PTFE at a rate exceeding about 10% per second. (emphasis in original)

No finding of the district court and no evidence of record establishes that that statement was made in reckless disregard of facts from which an intent to defraud may be inferred.

The district court's finding in 1982 that the 401 machine inherently stretched tape at some time in 1969 at a rate more than 10% per second, does not establish that Dr. Gore was aware of that fact in 1975, nor does it make untrue his statement that to his knowledge that had not been the rate of stretch employed. Nor does the district court's finding conflict with Dr. Gore's statement that the rate of stretching was neither measured nor controlled in the Gore shop before his invention of the claimed process as a whole.

Nor does the evidence of isolated statements support Garlock's contention that Dr. Gore attempted to convince the PTO that a physical phenomenon always existed in which stretching at a rate greater than 10% per second always produced a matrix tensile strength greater than 7300 psi. On the contrary, Dr. Gore set forth in his specification examples indicating that some samples broke, ruptured, or disintegrated.

(3) *Attorney's Fees*

The district court did not abuse its discretion in denying Garlock its request for attorney fees.

Infringement

[38] Where, as here, an appellate court reverses a holding of invalidity, and remand is ordered for trial of the factual issue of infringement, an inefficient use of judicial resources results if the second judgment is appealed. The better practice would therefore be for the district court to decide both the validity and infringement issues when both are contested at the trial, enabling the conduct of a single appeal and disposition of the entire case in a single appellate opinion.

Resolution of the infringement issue at trial may also overlap with resolution of the validity issue, where, for example, the claimed invention was or was not copied by the validity challenger, or the challenger substituted the claimed invention for freely available prior art processes or products, Eibel, supra, 261 U.S. at 56, or an assertion of nonenablement may conflict with the ease with which the accused infringer may be shown to have practiced the invention as taught in the patent. Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 61 (1923).

[39] The district court having declined to decide the infringement issue, Gore suggests that the record here is sufficient to warrant

our deciding it now. With reluctance in view of the length and bitter nature of the present litigation, we decline the suggestion. In so doing, we imply nothing of our view on the issue. Nor do we intend any implication that the district court could not itself determine the infringement issue on the present record. Infringement of particular claims of two patents was asserted. None of those claims has been finally held invalid. Assuming their continued assertion, infringement must be decided with respect to each asserted claim as

a separate entity. Altoona, supra, 294 U.S. at 487. Those factual determinations should be made in the first instance by the district court.

Decision

The holdings of invalidity of claim 1 of the '566 patent under §102(a) and of claim 17 of the '566 patent under §103, the determination that Gore did not commit fraud on the PTO, and the denial of attorney fees, are affirmed; the holdings that all claims of the '566 patent are invalid under §102(b), that claims 3 and 19 of the '566 patent are invalid under §103, and that all claims of the '566 patent are invalid under §112, are reversed. The holdings that claims 1, 9, 12, 14, 18, 35, 36, 43, 67, and 77 of the '390 patent are invalid under §§102 and 103, and that all claims of the '390 patent are invalid under §112, are reversed. The case is remanded for determination of the infringement issue.

Affirmed in part, reversed in part, and remanded .

Appendix

Appendix

Claims of the '566 patent discussed at trial:

1. A process for the production of a porous article of manufacture of a polymer of tetrafluoroethylene which process comprises expanding a shaped article consisting essentially of highly crystalline poly (tetrafluoroethylene) made by a paste-forming extrusion technique, after removal of lubricant, by stretching said unsintered shaped article at a rate exceeding about 10% per second and maintaining said shaped article at a temperature between about 35°C. and the crystalline melt point of said tetrafluoroethylene polymer during said stretching.

3. The process of claim 1 in which the rate of stretch is about 100% per second.

17. The process of claim 1 in which the shaped article is expanded such that its final length in the direction of expansion is greater than about twice the original length.

19. The process of claim 17 in which said final length is greater than about five times the original length.

Claims of '390 patent discussed at trial:

1. A porous material consisting essentially of highly crystalline polytetrafluoroethylene polymer, which material has a microstructure characterized by nodes interconnected by fibrils and has a matrix tensile strength in at least one direction above about 73,00 psi.

9. A porous material consisting essentially of polytetrafluoroethylene polymer, which material has a microstructure characterized by nodes interconnected by fibrils and has a matrix tensile strength in at least one direction above 9290 psi, which material has been heated to a temperature above the crystalline melt point of said polymer and has a crystallinity below about 95%.

12. A porous material in accordance with claim 9 which is in the form of a shaped article.

14. A product in accordance with claim 12 which is in the form of a film.

18. A product in accordance with claim 12 which is in the form of

continuous filaments.

35. A laminated structure comprising (a) a first shaped article formed of a porous material made of a tetrafluoroethylene polymer, which material has a microstructure characterized by nodes interconnected by fibrils and has a matrix tensile strength in at least one direction above about 7,300 psi, and (b) a second shaped article bonded to said first shaped article.

36. The structure of claim 35 in which said first shaped article is formed of a porous material which has a matrix tensile strength in at least one direction of at least 9290 psi, and has a crystallinity below about 95%.

43. A porous material made of a tetrafluoroethylene polymer, which material has a microstructure characterized by nodes interconnected by fibrils, which material (a) has a matrix tensile strength in at least one direction above about 9290 psi, (b) has been heated to a temperature above 327° C. and has a crystallinity below about 95%, and (c) has a dielectric constant of 1.2-1.8.

67. An impregnated structure comprising

(a) a shaped article formed of a porous material made of a tetrafluoroethylene polymer which material has a microstructure characterized by nodes interconnected by fibrils and a matrix tensile strength in at least one direction above about 9290 psi, and

(b) a polymer impregnated within the pores of the said shaped article.

77. The structure of claim 35 in which the first shaped article is a sheet having pores that will pass a gas but will not pass liquid water.

Footnotes

Footnote 1. 35 U.S.C. §102(a) and (b) provide:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or * * *

35 U.S.C. §103 provides:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. §112 provides:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. A claim may be written in independent or dependent form, and if in dependent form, it shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim.

Concurring/Dissenting Opinion Text

Concurrence/Dissent By:

Davis, Circuit Judge, concurring in the result in part and dissenting in part.

I concur in the result on (1) the validity of the '390 patent under §§ 102-103; (2) the validity of the '390 patent under §112; (3) the invalidity of claims 1 and 17 of the '566 patent; (4) lack of fraud on the Patent and Trademark Office; and (5) denial of attorneys' fees. I disagree and dissent as to the validity of claims 3 and 19 of the '566 patent.

1. The process invention embodied in claim 1 of the '566 patent was known, through use of the 401 machine in the Gore shop, well before the "invention date" (claimed by Robert Gore, the inventor) of October 1969. [1] As such, the claimed invention was invalid on at least three grounds: (i) it was anticipated and therefore would have been obvious (under 35 U.S.C. §103) at the time of the claimed invention date; (ii) the invention was "in public use" by the Gore shop (under 35 U.S.C. §102(b)) more than one year prior to the patent application (i.e., prior to May 21, 1969); and (iii) the invention (made by Robert Gore) was known to and used "by others in this country" (35 U.S.C. §102(a)) before the claimed invention date of October 1969, i.e. the invention was used by Wilbert Gore and others in the Gore shop before the October date. [2]

The critically important aspect of the invention of the '566 patent is the stretching of PTFE at a rate above 10% per second. [3] Robert Gore testified that he conceived this invention no earlier than October 1969 (and we have the right to take him at his word), [4] but the facts found by the District Court plainly show that the Gore shop was in fact practicing that invention considerably earlier.

The District Court found that in the 401 machine the distance between the stretch rollers controls the rate of stretch; a shorter distance results in a higher rate of stretch; for the process described in the '915 patent to be practiced with a rate of stretch *below* 10% per second, the distance between the stretch rollers would have to be greater than five feet; if the distance is less than four feet, the rate of stretch is greater than 10% per second; the machine drawings used to construct the 401 machine indicate that the distance between the stretch rollers was eight *inches* ; a Gore employee testified that "I am reasonably sure that no effective [stretch] rolls in question would have been more than three feet simply because of the nature and size of the equipment" and that he did

not remember any stretching more than three feet; another Gore employee testified that the distance between the rollers was "a maximum of 18 *inches* " (emphasis added); a document prepared by the same employee (an engineer) on June 10, 1969 reports that the stretch span was 8 *inches* ; the 401 machine was the only stretching machine used by the Gore company; and the 401 machine was never substantially changed before October 1969. All this adds up to the fact that the 401 machine was at all relevant times operated with a stretch of less than four feet. [5] There is no question that the machine was so operated before October 1969 (the District Court found that sales of tape made by the 401 machine were proposed in August 1969).

I can accept Robert Gore's affidavit (to the PTO) that there was no stretching in the Gore shop at a rate exceeding about 10% per second prior to "my invention disclosed in the captioned patent application" (emphasis added) [6] only because that declaration was expressly qualified by the phrase "to my knowledge" (emphasis added). The District Court specifically found no specific intent by Robert Gore to defraud and, on this record, we

cannot properly overturn that finding. But the absence of personal intent to defraud does not mean or say that, whether Robert Gore realized it or not, the 401 machine was not actually operating, well before October 1969, to stretch unsintered PTFE at a rate exceeding about 10% per second. Cf. O'Brien v. Westinghouse Electric Corp., 293 F.2d 1, 10 (3rd Cir. 1961). It seems impossible to me to reconcile Robert Gore's insistence on two facts--that (i) he invented the process in October 1969 and (ii) he had no knowledge prior to October 1969 of stretching PTFE at the critical rate--with the solid facts in the record as to the prior operation of the 401 machine, except on the view that Robert Gore did not realize that he and others in the Gore shop had made his invention previously.

2. It follows that in October 1969 the invention of '566 would have been obvious under §103 to Robert Gore because the prior practice of the 401 machine constituted prior art. Even if this was not prior art technically within §102, that statutory provision "is not the *only* source of prior art." In re Fout, 675 F.2d 297, 300 (CCPA 1982, emphasis in original). The 401 machine was practiced under the '915 patent (issued to Wilbert Gore) and, whether or not Robert Gore subjectively realized what was happening, he and others in the Gore shop were practicing the invention later embodied in the '566 patent. That was prior art at least as to Robert Gore. Id. at 300-01. [7]

3. If it be thought necessary to invoke §102 directly, in order to show anticipation, the record contains proof that the 401 machine was designed, constructed and used (just as described supra) in November and December 1968 and the early months of 1969--more than one year prior to the '566 patent application of May 21, 1970. See Jt. App. E 1199-E 1200. Section 102(b) therefore applies. Although commercial production was apparently not actively sought until June 1969, the practicing of the 401 machine prior to May 21, 1969 was "a public use" because the Gore company made "use of the device * * * in the factory in the regular course of business." Connecticut Valley Enterprises, Inc. v. United States, 348 F.2d 949, 952, 146 USPQ 404, 406 (Ct. Cl. 1965).

4. Also, §102(a) [8] applies here because Robert Gore was the inventor in the '566

patent and Wilbert Gore and others in the Gore shop were using the 401 machine before October 1969. Wilbert Gore (the inventor in the '915 patent under which the 401 machine was made and used) and the other employees are "others" within §102(a)--they are not the same as Robert Gore who claimed to be inventor of the process that ripened into the '566 patent. [9] See also §102(f), which would bar Robert Gore if he did not himself invent the subject matter of the '566 patent. [10]

5. The majority sustains the validity of claims 3 and 19 of the '566 patent (the claims also involved in appellant's suit for infringement) which are dependent on invalid claim 1. Because of the invalidity of claim 1 the only possible novelty in claim 3 would be the requirement that the rate of stretch would be about 100% per second, and the possible novelty of claim 19 would be that the final length would be greater than about five times the original length. My position is that both of these added elements, if novel, would have been obvious to persons of ordinary skill in the art.

The defect in the majority's analysis is that it neglects the cardinal fact that the prior art included the 401 machine (discussed supra), not merely the earlier patents assessed in the majority opinion. The 401 machine directly involved PTFE itself, not conventional thermoplastic polymers. That machine also directly involved rapid stretching of PTFE at a rate markedly exceeding 10%. With this prior art of the 401 machine before him, an ordinary person skilled in the art would maximize stretch rate, if only to improve the machine's production rate. Cf. In re Dwyer, Jewell, Johnson, McGrath, & Rubin, 317 F.2d 203, 207, 137 USPQ 540 (CCPA 1963). Moreover, the very existence and operation of the 401 machine, which stretched PTFE rapidly without breaking, suggests to the skilled person the probability of stretching at even higher rates. Certainly, in the light of the 401 machine, skilled workers would see in at least

the prior Markwood, Nash, and Scarlett patents (teaching extensive and rapid stretching of non-PTFE thermoplastics) the suggestion that the method of the 401 machine could also be used for comparable rapid and extensive stretching of PTFE.

6. In sum, I cannot escape the conclusion that--although there was no fraud proved--if the true facts as to the 401 machine had been made known to the PTO (as it requested), the involved claims of the '566 patent should (and probably would) not have been accepted.

Footnotes

Footnote 1. The 401 machine was used under the prior '915 patent (issued to Wilbert Gore) which contains no reference to the significance of the rate of stretch.
Footnote 2. Aside from the bases I discuss, I do not reach the other grounds asserted for invalidity of the '566 patent.
Footnote 3. Before the PTO Robert Gore concededly referred to this as "critical" to his invention or as *his* "invention."
Footnote 4. The District Court found that October 1969 was the earliest date Robert Gore asserts for his conception of the invention in the '566 patent.

Footnote 5. The Gores (Robert and Wilbert) testified at trial that the distance was five feet but there is no indication that the trial court (which did not cite this testimony but did cite the opposing evidence) credited the Gores' testimony.
Footnote 6. The factor of the rate of stretching was of direct interest to the examiner during the prosecution of the '566 patent. In response to the examiner's express request for a declaration that the Gore firm's production of stretched PTFE tape, prior to Robert Gore's invention asserted here, did not involve stretching of unsintered PTFE at a rate exceeding about 10% per second, Robert Gore filed an affidavit in the PTO specifically stating that " *to my knowledge* " (emphasis added) the 401 machine did *not* involve stretching at a rate exceeding about 10% per second.
Footnote 7. The District Court has found that there are no differences between claim 1 of the '566 patent and the processes previously used by the Gore firm to produce paste-extruded unsintered PTFE.
Footnote 8. An invention is anticipated if it "was known or used *by others* in this country * * * before the invention thereof by the applicant for patent" (emphasis added).
Footnote 9. It is undisputed that it was Wilbert Gore who initiated the project for the 401 machine and watched over it.
Footnote 10. The majority's discussion of "secondary considerations," though it is relevant to other aspects of this case, is irrelevant to the issue of anticipation raised by the 401 machine, and hardly persuasive as to the issues of obviousness based on or with respect to the 401 machine.

- End of Case -

Intellectual Property Library ISSN 1526-8535

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FULL TEXT OF CASES (USPQ2D)
All Other Cases

In re Jones (CA FC) 21 USPQ2d 1941 In re Jones

U.S. Court of Appeals Federal Circuit
21 USPQ2d 1941

Decided February 28, 1992
No. 91-1380

Headnotes

PATENTS

1. Patentability/Validity -- Obviousness -- Relevant prior art -- Particular inventions (§ 115.0903.03)

Claimed novel salt of acid commonly known as "dicamba" is not so closely related in structure to substituted ammonium salts disclosed in prior patent as to be prima facie obvious, since claimed salt is primary amine with ether linkage, whereas diethanolamino salt disclosed in reference patent is secondary amine without ether linkage, since claimed salt is plainly acyclic or linear, whereas morpholino salt, which is only substituted ammonium salt of dicamba with ether linkage disclosed in reference patent, is cyclic in structure, and since isopropylamino salt disclosed in reference patent is primary amine, but has iso-structure quite different from that of claimed salt.

2. Patentability/Validity -- Obviousness -- Relevant prior art -- Particular inventions (§ 115.0903.03)

Claimed novel salt of acid commonly known as "dicamba" cannot be held prima facie obvious in view of salts disclosed in prior patent, even though claimed salt is member of

genus of substituted ammonium salts broadly disclosed in reference patent, since reference discloses potentially infinite genus of "substituted ammonium salts" of dicamba, and lists several such salts, but does not specifically disclose salt claimed in application, and since claimed salt is not sufficiently similar to those disclosed in reference as to render it prima facie obvious.

3. Patentability/Validity -- Obviousness -- Combining references (§ 115.0905)

Contention that one skilled in herbicidal art would have been motivated to use, with acid commonly known as "dicamba," substituted ammonium salt such as that disclosed in two prior references does not warrant holding that claimed substituted ammonium salt of dicamba for use as herbicide is prima facie obvious, since there is no suggestion for combining disclosures of those references either in references themselves, which are directed to shampoo additives and production of morpholine, respectively, or in knowledge generally available to those skilled in art.

Case History and Disposition:

Page 1941

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Rita S. Jones, Michael T. Chirchirillo and Johnny L. Burns, serial no. 07/099,279 (the 2-(2 '-aminoethoxy)-ethanol salt of dicamba). From decision upholding rejection of only claim in application, applicants appeal. Reversed.

Attorneys:

Melvyn M. Kassenoff, East Hanover, N.J. (Gerald D. Sharkin and Richard E. Villa, East Hanover; Joanne M. Giesser, Palo Alto, Calif., with him on brief), for appellant.

Harris A. Pitlock, associate solicitor (Fred E. McKelvey, solicitor, with him on brief; Richard E. Schafer, of counsel), for appellee.

Page 1942

Judge:

Before Rich, Archer, and Clevenger, circuit judges.

Opinion Text

Opinion By:

Rich, J.

Rita S. Jones et al. (collectively Jones) appeal from the April 15, 1991 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), Appeal No. 90-1920, sustaining the rejection of claim 1, the only claim of application Ser. No. 07/099,279, titled "The 2-(2 '-Aminoethoxy) -- Ethanol Salt of Dicamba," as unpatentable under 35 USC 103. We conclude that the PTO has not presented a *prima facie* case of obviousness, and therefore *reverse* .

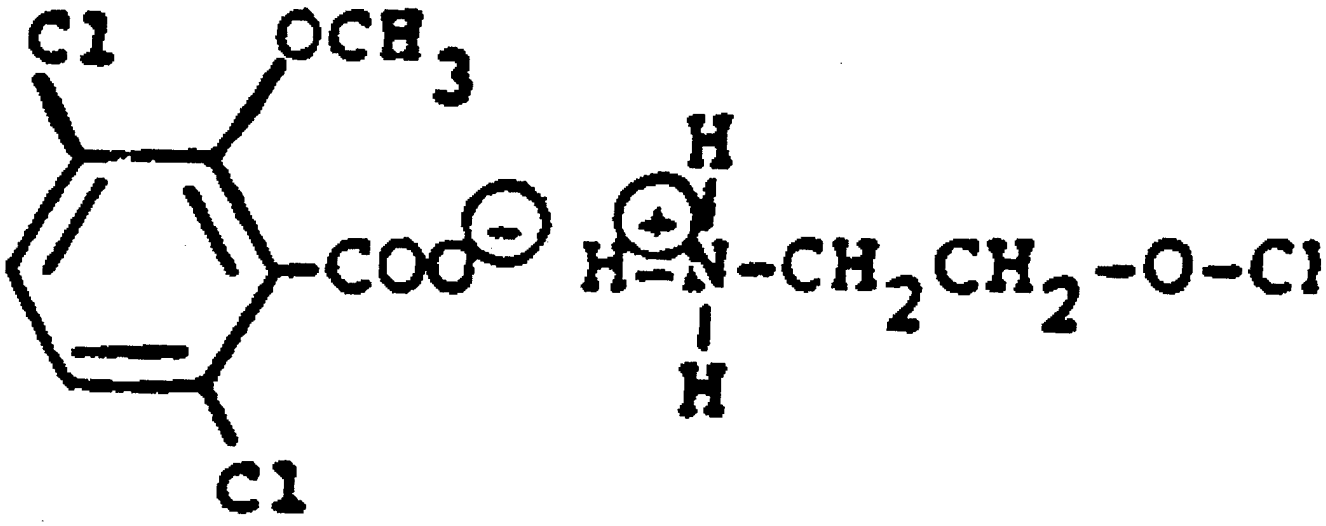
The Invention

The Claimed invention is a novel salt of 2-methoxy-3, 6-dichlorobenzoic acid, which acid is commonly referred to as "dicamba." A known herbicide, dicamba has typically been sold in the form of its known dimethylamine salt.

The sole claim of the application on appeal reads:

1. The 2-(2 '-aminoethoxy) ethanol salt of dicamba.

The claimed salt has the following structure:



The Rejection

Claim 1 stands rejected as obvious in view of the combined teachings of the following references:

Richter, U.S. Patent No. 3,013,054, Dec. 12, 1961

Moyle et al., U.S. Patent No. 3,056,669, Oct. 2, 1962

Balassa, U.S. Patent No. 3,725,031, Apr. 3, 1973

Zorayan et al., 88 *Chem. Abstracts* No. 52300j, 1978
Wideman, 86 *Chem. Abstracts* No. 43711a, 1977
Richter, which all agree is the closest prior art, discloses dicamba in free acid, ester, and salt forms, for use as a herbicide. Among the salt forms disclosed are substituted ammonium salts, a genus which admittedly encompasses the claimed salt. Richter does not specifically disclose the claimed 2-(2 '- aminoethoxy) ethanol salt, however. Most notably, Richter discloses (emphasis and bracketed word ours):

Compositions in which X is substituted ammonium are amine salts of 2-methoxy-3, 6-dichlorobenzoic acid [dicamba] and are prepared by the addition of the free acid to various amines. Typical amines which can be used to prepare such amine salts are dimethylamine, trimethylamine, triethylamine, diethanolamine, triethanolamine, isopropylamine, morpholine, and the like. *The resulting products are, respectively, the dimethylamino, trimethylamino, triethylamino, diethanolamino, triethanolamino, isopropylamino, and morpholino salts of 2-methoxy-3, 6-dichlorobenzoic acid.*

Zorayan teaches the amine (H [inf 2] N (CH [inf 2] CH [inf 2] O) [inf 2] H) used to make the claimed salt, as well as the use of that amine in the preparation of surfactants for shampoos, bath preparations, and emulsifiers.

Wideman also teaches the amine disclosed in Zorayan.

The content of the remaining references is unnecessary to our decision.

The Board upheld the examiner's rejection of claim 1 as obvious, finding that the claimed 2-2 '-aminoethoxy) ethanol salt of dicamba and the diethanolamine salt of dicamba specifically disclosed by Richter were "closely related in structure," and that based upon the expectation that "compounds similar in structure will have similar properties," a *prima facie* case of obviousness had arisen. The Board found that Jones' rebuttal evidence (Rule 132 declarations and data reported in the specification) failed to "compare the claimed subject matter with the closest prior art," and accordingly did not serve to rebut the *prima facie* case. This appeal followed.

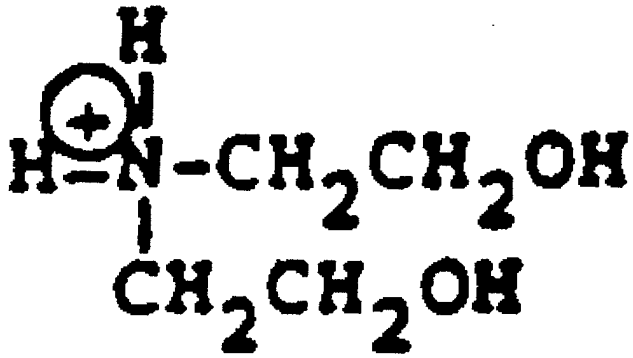
Analysis

The Solicitor contends that the claimed salt falls within the genus of substituted amine salts of dicamba disclosed by Richter, and that, like Richter's genus, the claimed compound has herbicidal activity. Thus, the Solicitor urges, under the circumstances of this case, (1) the genus/species relationship and (2) the common utility of the claimed and prior art compounds support the Board's holding of *prima facie* obviousness. Moreover, the Solicitor adds, although the claimed compound is neither a homolog nor a position isomer of those salts specifically disclosed in Richter, it is structurally similar thereto, particularly the diethanolamino salt noted by the Board.

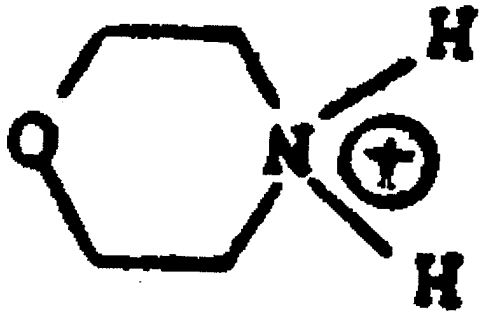
The question of "structural similarity" in chemical patent cases has generated a body of patent law unto itself. 1 Particular types or categories of structural similarity without more have, in past cases, given rise to *prima facie* obviousness; *see, e.g., In re Dillon*, 919 F.2d 688, 692-94, 16 USPQ2d 1897, 1900-02 (Fed. Cir. 1990) (tri-orthoesters and tetra-orthoesters), *cert. denied*, ___ U.S. ___, 111 S. Ct. 1682 (1991); *In re May*, 574

F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers); *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologs and structural isomers); *In re Hoch*, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). However, none of these types of structural similarity are involved here. And in any event, this court has previously stated that generalization is to be avoided insofar as specific structures are alleged to be *prima facie* obvious one from the other. *In re Grabiak*, 769 F.2d 729, 731, 226 USPQ 870, 872 (Fed. Cir. 1985).

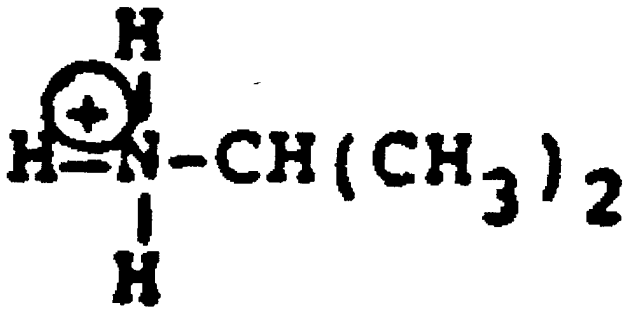
[1] On the basis of the record before us, we cannot sustain the Board's conclusion that the claimed salt and the diethanolamino salt disclosed by Richter are so "closely related in structure" as to render the former *prima facie* obvious in view of the latter. The claimed salt is a primary amine with an ether linkage. The diethanolamino salt disclosed by Richter is a secondary amine, without an ether linkage:



In addition, the only substituted ammonium salt of dicamba expressly disclosed by Richter having an ether linkage is the morpholino salt, which is *cyclic* in structure:



The claimed salt is, plainly, *a* cyclic; i.e., linear. Lastly, while the isopropylamino salt disclosed by Richter is a primary amine, as is the claimed salt, its iso- structure is quite different:



[2] The lack of close similarity of structure is not negated by the fact that the claimed salt is a member of Richter's broadly disclosed genus of substituted ammonium salts of dicamba. The Solicitor contends that " [t]he relative size of the genus disclosed by the prior art would not appear to be a controlling factor in determining whether a *prima facie* case of obviousness exists for a species encompassed within the described genus," citing *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 806-09, 10 USPQ2d 1843, 1845-48 (Fed. Cir.), *cert. denied*, ___ U.S. ___, 110 S. Ct. 498 (1989). We decline to extract from *Merck* the rule that the Solicitor appears to suggest -- that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it. In *Merck*, at issue on appeal was whether claims to a composition of two diuretics, amiloride and hydrochlorothiazide, present in a particular "medically synergistic" weight ratio, would have been obvious in view of a specific prior art disclosure of amiloride in combination with hydrochlorothiazide, one of 1200 such combinations disclosed in the prior art reference. *Id.* at 806, 10 USPQ2d at 1845. Based on the facts before it, including evidence at trial that the experimentation needed to arrive at the claimed dosage was "nothing more than routine," *Id.* at 809, 10 USPQ2d at 1847, the court affirmed the trial court's determination of obviousness. In contrast, though Richter discloses the potentially infinite genus of "substituted ammonium salts" of dicamba, and lists several such salts, the salt claimed here is not specifically disclosed. Nor, as we have explained above, is the claimed salt sufficiently similar in structure to those specifically disclosed in Richter as to render it *prima facie* obvious. Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts.

[3] The Solicitor points out that, given the breadth of forms of dicamba (free acid, ester, or salt) disclosed by Richter as having herbicidal utility, one of ordinary skill in the art would appreciate that the dicamba group has significance with respect to imparting herbicidal activity to dicamba compounds. Thus, the Solicitor contends, one skilled in the art would have been motivated to use, with dicamba, substituted ammonium salts made from a known amine, such as the amine disclosed by Zorayan and Wideman, and would have expected such a salt to have herbicidal activity. Before the PTO may combine the disclosures of two or more prior art references in order to establish *prima facie* obviousness, there must be some sug

gestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). We see no such suggestion in Zorayan, which is directed to shampoo additives, nor in Wideman, which teaches that the amine used to make the claimed compound is a byproduct of the production of morpholine. Nor does the broad disclosure of Richter fill the gap, for the reasons discussed above. Conspicuously missing from this record is any *evidence* , other than the PTO's speculation (if it be called evidence) that one of ordinary skill in the herbicidal art would have been motivated to make the modifications of the prior art salts necessary to arrive at the claimed 2-(2 '-aminoethoxy) ethanol salt. *See Grabiak*, 769 F.2d at 731-32, 226 USPQ at 872 ("[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/ [claimed] thioester change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant."): *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.")

Conclusion

We conclude that the PTO did not establish a *prima facie* case of obviousness, and thus did not shift to Jones the burden of coming forward with unexpected results or other objective evidence of non-obviousness. Accordingly, the decision of the Board is *REVERSED.*

Footnotes

Footnote 1. *See generally* Helmuth A. Wegner, "Prima Facie Obviousness of Chemical Compounds," 6 *Am. Pat. L. Assoc. O. J.* 271 (1978).

- End of Case -

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FULL TEXT OF CASES (USPQ2D)
All Other Cases

In re Mills (CA FC) 16 USPQ2d 1430 In re Mills

U.S. Court of Appeals Federal Circuit
16 USPQ2d 1430

Decided October 9, 1990
No. 90-1184

Headnotes

PATENTS

1. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Apparatus which produces aerated cementitious composition by driving output pump for its mixing chamber at capacity greater than feed rate of ingredients into mixing chamber, and thereby drawing air into composition, is not obvious in view of prior patent for mixing apparatus, even though device of prior patent provides for regulation of flow rate into mixing chamber, since patent contains no suggestion or motivation for overdriving output pump so as to entrain air in mixed ingredients.

2. Patentability/Validity - Anticipation - In general (§ 115.0701)

Patentability/Validity - Obviousness - Relevant prior art - In general (§ 115.0903.01)

Board of Patent Appeals and Interferences erred by requiring applicant to show that prior

art reference lacked functional characteristics of claimed device, since even though such requirement would be proper for rejection based on lack of novelty, it is not pertinent whether prior art device possesses claimed invention's functional characteristics if, as here, application was rejected on basis of obviousness and reference does not describe or suggest claimed invention's structure.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Peter S. Mills, serial no. 891,374, continuation of serial no. 607-805, filed May 4, 1984. From decision upholding examiner's rejection of claims 6-9 and 11-14, applicant appeals. Reversed.

Attorneys:

James C. Wray, McLean, Va, for appellant.

Muriel E. Crawford, assistant solicitor (Fred E. McKelvey, solicitor, with her on brief), for appellee.

Judge:

Before Miller, senior circuit judge, and Mayer and Lourie, circuit judges.

Opinion Text

Opinion By:

Lourie, J.

This appeal is from the November 2, 1989, decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (Board), Appeal No. 88-0141, affirming the examiner's rejection, under 35 U.S.C. §103, of claims 6-9 and 11-14 in Mills' application Serial No. 891,374, a continuation of Serial No. 607-805, filed May 4, 1984, entitled "Methods of and Apparatus for Producing Aerated Cementitious Compounds." The remainder of the claims (1-5, 10, and 15) have all been cancelled. We reverse.

I

BACKGROUND

A. *The Invention*

Mills' claimed invention is an apparatus for producing aerated cementitious compositions. Claim 6 is the broadest claim:

6. Apparatus for producing an aerated cementitious composition, comprising
a mixing chamber being open to atmosphere and containing mixing means,
feed means for feeding ingredients comprising cement, foaming agent and liquid to the mixing chamber,
mixing means for mixing ingredients fed to the mixing chamber, pump means for pumping the mixed ingredients to a desired site and having a pump inlet connected to an outlet of the mixing chamber,
drive motor means connected through gearbox means providing a pumping capacity of the pump means greater than the feed rate of the ingredients to the mixing chamber provided by the feed means, such that in operation air is drawn into the mixing chamber, and entrained in the mixed ingredients.

The essence of Mills' invention is the machine's ability to aerate a cementitious composition by driving the output pump at a capacity greater than the feed rate, thereby drawing air into the composition. This aeration produces a composition with substantially lower density than standard cementitious composition mixing ingredients.

B. *The Reference*

The sole reference upon which the Board relied in affirming the examiner's rejection was Mathis et al. U.S. Patent 4,117,547 (Mathis). 1 Mathis discloses a mixing chamber which is open to the atmosphere and which contains a mixing means. Two feed means for feeding ingredients in the mixing chamber are provided. The first feed means may consist of a screw conveyer and the second, a flow metering device such as an adjustable valve. A pump means pumps the mixture from the mixing chamber to a desired site and a drive motor means is connected to mixing means and pump means. A separate motor drives the feed means.

A control system exists to arrest the feed means so as not to overfill the mixing chamber. This system comprises a level detector in the mixing chamber, which signals the feed means to close when the mixing chamber stores the predetermined maximum permissible quantity of material.

C. *The Rejection*

The Board affirmed the examiner's Section 103 rejection of claims 6-9 and 11-14, "finding correspondence in the Mathis reference for all of the subject matter recited in the appellants' claims. ..." With regard to Mills' claim language relating to aerating the mixture, the Board stated: "[i]n our opinion, the differences between claim 6 and the

Mathis machine ... lie solely in the functional language of the claim." The Board further found that Mathis teaches the use of separate input and output motors in order to permit the various mixing means and pumps to operate at different rates, and that Mathis "contemplates a situation wherein the rate of the outlet pump would be greater than the inlet pumps...." The Board concluded on this point: "[w]e are of the opinion that the Mathis machine is capable of being operated in such a fashion as to cause [the output] pump 18 to draw air into the mixing chamber 17 so that it is entrained in the mixture." The Board also agreed with Mills' contention that Mathis is not directed to the problem of producing aerated cementitious material, but noted that Mills is not claiming a method, but an apparatus, and all of Mills' apparatus structure is present in the Mathis machine.

II

DISCUSSION

All of the rejected claims are apparatus claims. The Board found "correspondence in the Mathis reference for all of the subject matter recited in appellants' claims" and that "[t]he Mathis machine discloses all of the structure set forth in claim 1" (a method claim not before us). It asserts that the use of such a mechanism would have been obvious and that the differences between claim 6 and the Mathis machine lie solely in the functional language of the claim, the preamble merely stating an intended use for the machine. This language suggests a lack of novelty rejection under 35 U.S.C. §102, rather than an obviousness rejection. However, no Section 102 rejection has been made or is before us. What is before us is a rejection for obviousness, and we must decide whether the Board erred in that rejection.

We note first that nonobviousness is a question of law to be determined from the facts. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). We review the Board's determination of obviousness, based on the scope and content of the Mathis reference and the differences between the Mathis reference and the Mills claims, for correctness or error. *In re Carleton,* 599 F.2d 1021 1024 n.14, 202 USPQ 165 , 169 n.14 (CCPA 1979).

[1] After reviewing the record, the arguments in the briefs, and the Mathis reference, we conclude that Mathis would not have rendered the claimed invention obvious. The closest Mathis comes to suggesting Mills' claimed apparatus is at column 3, lines 42-47, which states

he rate at which the inlet 2b receives a solid constituent depends on the speed of the feed screw 4. Such speed can be regulated by a prime mover 6 which includes a variable-speed transmission.

This brief reference contains no suggestion of "pump means and the feed means providing a pumping capacity of the pump means greater than the feed rate of ingredients to the mixing chamber provided by the feed means, such that in operation air is drawn into the mixing chamber, and air entrained in the mixed ingredients," as provided for in Mills' claim 6. While Mathis' apparatus may be capable of being modified to run the way Mills' apparatus is claimed, there must be a suggestion or motivation in the reference to do so. *See In re Gordon,* 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

We see no such suggestion. The apparatus claimed by Mills is different from that of Mathis, since the fact that motor 6 of Mathis (the feed means) can be run at a variable speed does not require that motor 20 (connected to the pump) be run at a lesser speed "such that in operation air is drawn into the mixing chamber and air entrained in the mixed ingredients."

[2] The Board found that the difference between the claimed subject matter and the prior art resided solely in functional language and that appellant had to show that the prior art device lacked the functional characteristics of the claimed device, citing *In re Ludtke,* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). *Ludtke,* however, dealt with a rejection for lack of novelty, in which case it was proper to require that a prior art reference cited as anticipating a claimed invention be shown to lack the characteristics of the claimed invention. That proof would in fact negate the assertion that the claimed invention was described in the prior art. We are here, however, facing an obvious

ness issue. It is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure. That is the case here. Given the facts before us, we hold that the Board was in error in affirming the examiner's rejection of claims 6-9 and 11-13 as obvious in view of Mathis, and we therefore *reverse* the Board.

REVERSED

Footnotes

Footnote 1. The examiner rejected the claims at issue under 35 U.S.C. §103 as being unpatentable not only over Mathis but also in view of Gibson et al. U.S. Patent 2,717,770. However, the Board affirmed the examiner's rejection of claims 6-9 and 11-14 based solely on the Mathis reference. With regard to Gibson the Board stated:

We view the teachings of Gibson at best as being merely confirmatory of the fact that aerated mixtures can be produced by machines in which a pump means operates upon a mixing chamber at a greater rate than the ingredients are fed thereunto so that air is drawn into the mixing chamber and entrained in the mixed ingredients.

App. 2.

- End of Case -

Intellectual Property Library ISSN 1526-8535

FULL TEXT OF CASES (USPQ2D)
All Other Cases

In re Vaeck (CA FC) 20 USPQ2d 1438 In re Vaeck

U.S. Court of Appeals Federal Circuit
20 USPQ2d 1438

Decided October 21, 1991
No. 91-1120

Headnotes

PATENTS

1. Patentability/Validity - Obviousness - Combining references (§ 115.0905)

Rejection of claimed subject matter as obvious under 35 USC 103 in view of combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that such person would have reasonable expectation of success; both suggestion and reasonable expectation of success must be founded in prior art, not in applicant's disclosure.

2. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Patent and Trademark Office has failed to establish prima facie obviousness of claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, since prior art does not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill reasonable expectation of success in doing so;

expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious expression of unrelated genes in cyanobacteria for unrelated purposes.

3. Patentability/Validity - Specification - Enablement (§ 115.1105)

JUDICIAL PRACTICE AND PROCEDURE

Procedure - Judicial review - Standard of review - Patents (§ 410.4607.09)

Specification must, in order to be enabling as required by 35 USC 112, first paragraph, teach person skilled in art to make and use invention without "undue experimentation," which does not preclude some experimentation; enablement is question of law which is reviewed independently on appeal, although such determination is based upon underlying factual findings which are reviewed for clear error.

PATENTS

4. Patentability/Validity - Specification - Enablement (§ 115.1105)

Patent and Trademark Office did not err in rejecting, as non-enabling pursuant to 35 USC 112, first paragraph, claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, in view of relatively incomplete understanding of biology of cyanobacteria as of applicants' filing date, as well as limited disclosure by applicants of particular cyanobacterial genera operative in claimed invention, since there is no reasonable correlation between narrow disclosure in applicants' specification and broad scope of protection sought in claims encompassing gene expression in any and all cyanobacteria.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent, serial no. 07/021,405, filed March 4, 1987, by Mark A. Vaeck, Wipa Chungjatupornchai, and Lee McIntosh (hybrid genes incorporating a DNA fragment containing a gene coding for an

insecticidal protein, plasmids, transformed cyanobacteria expressing such protein and method for use as a biocontrol agent). From decision rejecting claims 1-48 and 50-52 as unpatentable under 35 USC 103, and rejecting claims 1-48 and 50-51 for lack of enablement, applicants appeal. Affirmed and part and reversed in part; Mayer, J., dissents with opinion.

Attorneys:

Ian C. McLeod, Okemos, Mich., for appellant.

Teddy S. Gron, associate solicitor (Fred E. McKelvey, solicitor and Richard E. Schafer, associate solicitor, with him on brief), for appellee.

Judge:

Before Rich, Archer, and Mayer, circuit judges.

Opinion Text

Opinion By:

Rich, J.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 USC 103, as well as the rejection of claims 1-48 and 50-51 under 35 USC 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

BACKGROUND

A. *The Invention*

The claimed invention is directed to the use of genetic engineering techniques 1 for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus* proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being

consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.
As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote 2 kingdom, the

cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within transformed 3 cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.
More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing 4 the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.
The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:
1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:
(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and
(b) at least one DNA fragment coding for an insecticidally active protein produced by a Bacillus strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,
the DNA fragments being linked so that the gene is expressed.
Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers. 5 Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which expresses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

B. *Appellants' Disclosure*

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus* (*B. thuringiensis, B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis, Anacystis, Synechococcus, Agmenellum, Aphanocapsa, Gloecapsa, Nostoc, Anabaena* and *Ffremyllia*) as useful hosts.
The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular

insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis,* linked to (2) a particular promoter, the P Lpromoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P Lpromoter.

C. *The Prior Art*

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns, 6 the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT). 7 Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

Sekar I, 8 Sekar II, 9 and Ganesan 10 collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium, B. subtilis* and *E. coli.*

Friedberg 11 discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O LP Loperator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis* ...."

Miller 12 compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases 13 purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli.*

Nierzwicki-Bauer 14 identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbc* L, the large subunit of the enzyme ribulose-1, 5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.

Chauvat 15 discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

Reiss 16 studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

Kolowsky 17 discloses chimeric plasmids designed for transformation of the

cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.
Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

D. *The Grounds of Rejection*

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 USC 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus,* and the advantages of expressing such genes in heterologous 18 hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the

expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was prima facie obvious.
Additional rejections were entered against various groups of dependent claims which we need not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above.
The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 USC 112, first paragraph, on

the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) 19 and (z) 20 as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided in the specification. With respect to unpredictability, the examiner stated that

he cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis, Anacystis, Synechococcus, Agmenellum, Nostoc, Anabaena,* etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera. Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970)."

OPINION

A. *Obviousness*

We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 USC 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff,* 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990).

[1] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

[2] We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene

encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli.* While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed *bacterial* hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae. 21 Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes

the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins. In *O'Farrell,* this court affirmed an obviousness rejection of a claim to a method for

producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 USPQ2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 USPQ2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.

....

... Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 USPQ2d at 1679-80.

In contrast with the situation in *O'Farrell,* the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. *Enablement*

[3] The first paragraph of 35 USC 112 requires, *inter alia,* that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 USPQ2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 USPQ2d at 1402.

In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their

specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.
The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.
[4] Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification).

22 Accordingly, we affirm the § 112 rejection as to those claims.
In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt,* 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, 23 to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. *See Fisher,* 427 F.2d at 839, 166 USPQ at 24. In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.
Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera

Anacystis and *Synechocystis.* Claim 48, which depend from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria. Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

CONCLUSION

The rejection of claims 1-48 and 50-52 under 35 USC 103 is *reversed.* The rejection of claims 1-46 and 50-51 under 35 USC 112, first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed.*
AFFIRMED-IN-PART, REVERSED-IN-PART

Footnotes

Footnote 1. Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell,* 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988), and are not repeated here.
Footnote 2. All living cells can be classified into one of two broad groups, procaryotes and eucaryotes. The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus wherein their DNA resides.
Footnote 3. "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part of the host cyanobacteria, to be replicated as new cyanobacteria are generated.
Footnote 4. "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of DNA) via messenger RNA to ribosomes where a specific protein is made.
Footnote 5. In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.
Footnote 6. *Nucleic Acids Res.* 8917 (1984).
Footnote 7. Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.
Footnote 8. *Biochem. and Biophys. Res. Comm.* 748 (1986).
Footnote 9. *Gene* 151 (1985).
Footnote 10. *Mol. Gen. Genet.* 181 (1983).
Footnote 11. *Mol. Gen. Genet.* 505 (1986).
Footnote 12. *J. Bacteriology* 246 (1979).
Footnote 13. RNA polymerase, the enzyme responsible for making RNA from DNA, binds at specific nucleotide sequences (promoters) in front of genes in DNA, and then moves through the gene making an RNA molecule that includes the information

contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.
Footnote 14. *Proc. Natl. Acad. Sci. USA* 5961 (1984).
Footnote 15. *Mol. Gen. Genet.* 185 (1986).
Footnote 16. *Gene* 211 (1984).
Footnote 17. *Gene* 289 (1984).
Footnote 18. Denotes different species or organism.
Footnote 19. MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:
In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure....
Footnote 20. MPEP 796.03(z), "Undue Breadth," provides in part:
n applications directed to intentions in arts were the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol,* 1938 C.D. 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield,* 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...
Footnote 21. *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Procaryotae"). Procaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom; Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).
Footnote 22. The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan,* 559 F.2d 595, 605-07, 194 USPQ 527, 536-38 (CCPA 1977). *See also United States Steel Corp. v. Phillips Petroleum Co.,* 865 F.2d 1247, 1251, 9 USPQ2d 1461, 1464 (Fed. Cir. 1989) (citing *Hogan*); *Hormone Research Found., Inc. v. Genentech, Inc.,* 904 F.2d 1558, 1568-69, 15 USPQ2d 1039, 1047-48 (Fed. Cir. 1990) (directing district court, on remand, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of *Fisher*), *cert. dismissed,* — U.S. —, 111 S. Ct. 1434 (1991). We therefore do not consider the effect of *Hogan* and its progeny on *Fisher* 's analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher,* 427 F.2d at 839, 166 USPQ at 24.
Footnote 23. The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi,* 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

Dissenting Opinion Text

Dissent By:

Mayer, J., dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co.,* 832 F.2d 581, 584, 4 USPQ2d 1621, 1624 (Fed. Cir. 1987); *Eaton Corp. v. Appliance Valves Corp.,* 790 F.2d 874, 877, 229 USPQ 668, 671 (Fed. Cir. 1986). But that is precisely what the court has permitted here. The PTO conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if thought this opinion were more persuasive than the board's, I could not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co.,* 383 U.S. 1, 17, 148 USPQ 459, 467 (1966); *Jurgens v. McKasy,* 927 F.2d 1552, 1560, 18 USPQ2d 1031, 1037 (Fed. Cir. 1991). And "[w]here there are two permissible views of

the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City,* 470 U.S. 564, 574 (1985). The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff,* 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990); *In re Kulling,* 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1057 (Fed. Cir. 1990). There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.

- End of Case -

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2. 35 U.S.C. 102(e) as amended by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 (form paragraph 7.12) must be applied if the reference is one of the following:

a. a U.S. patent or a publication of a U.S. application for patent filed under 35 U.S.C. 111(a);

b. a U.S. patent issued directly or indirectly from, or a U.S. or WIPO publication of, an international application if the international application has **an international filing date on or after November 29, 2000.**

See the Examiner Notes for form paragraph 7.12 to assist in the determination of the 35 U.S.C. 102(e) date of the reference.

3. Pre-AIPA 35 U.S.C 102(e) (form paragraph 7.12.01) must be applied if the reference is a U.S. patent issued directly, or indirectly, from an international application filed prior to November 29, 2000. See the Examiner Notes for form paragraph 7.12.01 to assist in the determination of the 35 U.S.C. 102(e) date of the reference.

4. In determining the 35 U.S.C. 102(e) date, consider priority/benefit claims to earlier-filed U.S. provisional applications under 35 U.S.C. 119(e), U.S. nonprovisional applications under 35 U.S.C. 120 or 121, and international applications under 35 U.S.C. 120, 121 or 365(c) if the subject matter used to make the rejection is appropriately supported in the relied upon earlier-filed application's disclosure (and any intermediate application(s)). A benefit claim to a U.S. patent of an earlier-filed international application, which has an international filing date prior to November29, 2000, may only result in an effective U.S. filing date as of the date the requirements of 35 U.S.C. 371(c)(1), (2) and (4) were fulfilled. Do NOT consider any priority/benefit claims to U.S. applications which are filed before an international application that has an international filing date prior to November 29, 2000. Do NOT consider foreign priority claims under 35 U.S.C. 119(a)-(d) and 365(a).

5. If the reference is a publication of an international application (including voluntary U.S. publication under 35 U.S.C. 122 of the national stage or a WIPO publication) that has an international filing date prior to November 29, 2000, did not designate the United States or was not published in English by WIPO, do not use this form paragraph. Such a reference is not a prior art reference under 35 U.S.C. 102(e). The reference may be applied under 35 U.S.C. 102(a) or (b) as of its publication date. See form paragraphs 7.08 and 7.09.

6. In bracket 2, insert either --clearly anticipated-- or --anticipated-- with an explanation at the end of the paragraph.

7. In bracket 3, insert the prior art relied upon.

8. This form paragraph must be preceded by either of form paragraphs 7.12 or 7.12.01.

9. Patent application publications may only be used if this form paragraph was preceded by form paragraph 7.12.

<

¶ *7.16 Rejection, 35 U.S.C. 102(b), Public Use or on Sale*

Claim **[1]** rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention. **[2]**

Examiner Note:

1. This form paragraph must be preceded either by form paragraphs 7.07 and 7.09 or by form paragraph 7.103.
2. A full explanation of the evidence establishing a public use or sale must be provided in bracket 2.

¶ *7.17 Rejection, 35 U.S.C. 102(c), Abandonment of Invention*

Claim **[1]** rejected under 35 U.S.C. 102(c) because the invention has been abandoned. **[2]**

Examiner Note:

1. This form paragraph must be preceded either by form paragraph 7.07 and 7.10 or by form paragraph 7.103.
2. In bracket 2, insert a full explanation of the evidence establishing abandonment of the invention. See MPEP § 2134.

¶ *7.18 Rejection, 35 U.S.C. 102(d), Foreign Patenting*

Claim **[1]** rejected under 35 U.S.C. 102(d) as being barred by applicants **[2]**.

[3]

Examiner Note:

1. This form paragraph must be preceded either by form paragraphs 7.07 and 7.11 or by form paragraph 7.103.
2. In bracket 3, insert an explanation of this rejection which must include appropriate dates and how they make the foreign patent available under 35 U.S.C. 102(d).
3. Refer to MPEP § 2135 for applicable 35 U.S.C. 102(d) prior art.

¶ *7.19 Rejection, 35 U.S.C. 102(f), Applicant Not the Inventor*

Claim **[1]** rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. **[2]**

Examiner Note:

1. This paragraph must be preceded either by paragraphs 7.07 and 7.13 or by paragraph 7.103.
2. In bracket 2, insert an explanation of the supporting evidence establishing that applicant was not the inventor. See MPEP § 2137.

706.02(j) Contents of a 35 U.S.C. 103 Rejection

35 U.S.C. 103 authorizes a rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references. After indicating that the rejection is under 35 U.S.C. 103, the examiner should set forth in the Office action:

(A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate,

(B) the difference or differences in the claim over the applied reference(s),

(C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and

(D) an explanation why one of ordinary skill in the art at the time the invention was made would have been motivated to make the proposed modification.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). See MPEP § 2144 - § 2144.09 for examples of reasoning supporting obviousness rejections.

Where a reference is relied on to support a rejection, whether or not in a minor capacity, that reference should be positively included in the statement of the rejection. See *In re Hoch,* 428 F.2d 1341, 1342 n.3 166 USPQ 406, 407 n. 3 (CCPA 1970).

It is important for an examiner to properly communicate the basis for a rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply. Furthermore, if an initially rejected application issues as a patent, the rationale behind an earlier rejection may be important in interpreting the scope of the patent claims. Since issued patents are presumed valid (35 U.S.C. 282) and constitute a property right (35 U.S.C. 261), the written record must be clear as to the basis for the grant. Since patent examiners cannot normally be compelled to testify in legal proceedings regarding their mental processes (see MPEP § 1701.01), it is important that the written record clearly explain the rationale for decisions made during prosecution of the application.

See MPEP § 2141 - § 2144.09 generally for guidance on patentability determinations under 35 U.S.C. 103, including a discussion of the requirements of *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966). See MPEP § 2145 for consideration of applicant's rebuttal arguments. See MPEP § 706.02(l) - § 706.02(l)(3) for a discussion of prior art disqualified under 35 U.S.C. 103(c).

706.02(k) Provisional Rejection (Obviousness) Under 35 U.S.C. 102(e)/103 [R-1]

Effective November 29, 1999, subject matter which was prior art under former 35 U.S.C. 103 via 35 U.S.C. 102(e) is now disqualified as prior art against the claimed invention if that subject matter and the claimed invention "were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." This change to 35 U.S.C. 103(c) applies to all utility, design and plant patent applications filed on or after November 29, 1999, including continuing applications filed under 37 CFR 1.53(b), continued prosecution applications filed under 37 CFR 1.53(d), and reissues. The amendment to 35 U.S.C. 103(c) does not affect any application filed before November 29, 1999, a request for examination under 37 CFR 1.129 of such an application, nor a request for continued examination under 37 CFR 1.114 of such an application. >The changes to 35 U.S.C. 102(e) in the Intellectual Property and High Technology Technical Amendments Act of 2002 (Pub. L. 107-273, 116 Stat. 1758 (2002)) did not affect the exclusion under 35 U.S.C. 103(c) as amended on November 29, 1999.< See MPEP § 706.02(l)(1) for additional information regarding disqualified prior art under 35 U.S.C. 102(e)/ 103.

The Supreme Court reaffirmed and relied upon the *Graham* three pronged test in its consideration and determination of obviousness in the fact situations presented in *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 189 USPQ 449, *reh'g denied*, 426 U.S. 955 (1976) and *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 163 USPQ 673 (1969). In each case, the Court discussed whether the claimed combinations produced a "new or different function" and a "synergistic result," but it clearly decided whether the claimed inventions were nonobviousness on the basis of the three-way test in *Graham*. Nowhere in its decisions in these cases does the Court state that the "new or different function" and "synergistic result" tests supersede a finding of nonobvious or obviousness under the *Graham* test.

Accordingly, examiners should apply the test for patentability under 35 U.S.C. 103 set forth in *Graham*. See below for a detailed discussion of each of the *Graham* factual inquiries. It should be noted that the Supreme Court's application of the *Graham* test to the fact circumstances in *Ag Pro* was somewhat stringent, as it was in *Black Rock*. Note *Republic Industries, Inc. v. Schlage Lock Co.*, 592 F.2d 963, 200 USPQ 769 (7th Cir. 1979). The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540, 218 USPQ 871, 880 (Fed. Cir. 1983) that

> A requirement for "synergism" or a "synergistic effect" is nowhere found in the statute, 35 U.S.C. When present, for example in a chemical case, synergism may point toward nonobviousness, but its absence has no place in evaluating the evidence on obviousness. The more objective findings suggested in *Graham*, supra, are drawn from the language of the statute and are fully adequate guides for evaluating the evidence relating to compliance with 35 U.S.C. § 103. *Bowser Inc. v. United States*, 388 F. 2d 346, 156 USPQ 406 (Ct. Cl. 1967).

BASIC CONSIDERATIONS WHICH APPLY TO OBVIOUSNESS REJECTIONS

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

OBJECTIVE EVIDENCE MUST BE CONSIDERED

Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence. The weight to be accorded to the evidence depends on the individual factual circumstances of each case. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The ultimate determination on patentability is made on the entire record. *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

See MPEP § 716- § 716.06 for a discussion of objective evidence and its role in the final legal determination of whether a claimed invention would have been obvious under 35 U.S.C. 103.

2141.01 Scope and Content of the Prior Art

I. PRIOR ART AVAILABLE UNDER 35 U.S.C. 102 IS AVAILABLE UNDER 35 U.S.C. 103

"Before answering *Graham's* 'content' inquiry, it must be known whether a patent or publication is in the prior art under 35 U.S.C. § 102." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Subject matter that is prior art under 35 U.S.C. 102 can be used to support a rejection under section 103. *Ex parte Andresen*, 212 USPQ 100, 102 (Bd. Pat. App. & Inter. 1981) ("it appears to us that the commentator [of 35 U.S.C.A.] and the [con-

gressional] committee viewed section 103 as including all of the various bars to a patent as set forth in section 102.").

A 35 U.S.C. 103 rejection is based on 35 U.S.C. 102(a), 102(b), 102(e), etc. depending on the type of prior art reference used and its publication or issue date. For instance, an obviousness rejection over a U.S. patent which was issued more than 1 year before the filing date of the application is said to be a statutory bar just as if it anticipated the claims under 35 U.S.C. 102(b). Analogously, an obviousness rejection based on a publication which would be applied under 102(a) if it anticipated the claims can be overcome by swearing behind the publication date of the reference by filing an affidavit or declaration under 37 CFR 1.131.

For an overview of what constitutes prior art under 35 U.S.C. 102, see MPEP § 901 - § 901.06(d) and § 2121 - § 2129.

II. SUBSTANTIVE CONTENT OF THE PRIOR ART

See MPEP § 2121 - § 2129 for case law relating to the substantive content of the prior art (e.g., availability of inoperative devices, extent to which prior art must be enabling, broad disclosure rather than preferred embodiments, admissions, etc.).

III. CONTENT OF THE PRIOR ART IS DETERMINED AT THE TIME THE INVENTION WAS MADE TO AVOID HINDSIGHT

The requirement "at the time the invention was made" is to avoid impermissible hindsight. See MPEP § 2145, paragraph X.A. for a discussion of rebutting applicants' arguments that a rejection is based on hindsight.

"It is difficult but necessary that the decisionmaker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

IV. 35 U.S.C. 103(c) — EVIDENCE REQUIRED TO SHOW CONDITIONS OF 35 U.S.C. 103 APPLY

An applicant who wants to avail himself or herself of the benefits of 35 U.S.C. 103(c) has the burden of establishing that subject matter which qualifies as prior art under subsection (e), (f) or (g) of section 102 and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. *Ex parte Yoshino*, 227 USPQ 52 (Bd. Pat. App. & Inter. 1985). Note that for applications filed prior to November 29, 1999, 35 U.S.C. 103(c) is limited on its face to subject matter developed by another person which qualifies as prior art only under subsection (f) or (g) of section 102. See MPEP § 706.02(l)(1). See also *In re Bartfeld*, 925 F.2d 1450, 1453-54, 17 USPQ2d 1885, 1888 (Fed. Cir. 1991) (Applicant attempted to overcome a 35 U.S.C. 102(e)/103 rejection with a terminal disclaimer by alleging that the public policy intent of 35 U.S.C 103(c) was to prohibit the use of "secret" prior art in obviousness determinations. The court rejected this argument, holding "We may not disregard the unambiguous exclusion of § 102(e) from the statute's purview.").

See MPEP § 706.02(l)(2) for the requirements which must be met to establish common ownership.

2141.01(a) Analogous and Nonanalogous Art

TO RELY ON A REFERENCE UNDER 35 U.S.C. 103, IT MUST BE ANALOGOUS PRIOR ART

The examiner must determine what is "analogous prior art" for the purpose of analyzing the obviousness of the subject matter at issue. "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). See also *In re Deminski*, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986); *In re Clay*, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) ("A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's

endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); and *Wang Laboratories Inc. v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993).

PTO CLASSIFICATION IS SOME EVIDENCE OF ANALOGY, BUT SIMILARITIES AND DIFFERENCES IN STRUCTURE AND FUNCTION CARRY MORE WEIGHT

While Patent Office classification of references and the cross-references in the official search notes are some evidence of "nonanalogy" or "analogy" respectively, the court has found "the similarities and differences in structure and function of the inventions to carry far greater weight." *In re Ellis*, 476 F.2d 1370, 1372, 177 USPQ 526, 527 (CCPA 1973) (The structural similarities and functional overlap between the structural gratings shown by one reference and the shoe scrapers of the type shown by another reference were readily apparent, and therefore the arts to which the reference patents belonged were reasonably pertinent to the art with which appellant's invention dealt (pedestrian floor gratings).); *In re Clay*, 966 F.2d 656, 23 USPQ2d 1058 (Fed. Cir. 1992) (Claims were directed to a process for storing a refined liquid hydrocarbon product in a storage tank having a dead volume between the tank bottom and its outlet port wherein a gelled solution filled the tank's dead volume to prevent loss of stored product while preventing contamination. One of the references relied upon disclosed a process for reducing the permeability of natural underground hydrocarbon bearing formations using a gel similar to that of applicant to improve oil production. The court disagreed with the PTO's argument that the reference and claimed inventions were part of the same endeavor, "maximizing withdrawal of petroleum stored in petroleum reserves," and found that the inventions involved different fields of endeavor since the reference taught the use of the gel in a different structure for a different purpose under different temperature and pressure conditions, and since the application related to storage of liquid hydrocarbons rather than extraction of crude petroleum. The court also found the reference was not reasonably pertinent to the problem with which the inventor was concerned because a person having ordinary skill in the art would not reasonably have expected to solve the problem of dead volume in tanks for refined petroleum by considering a reference dealing with plugging underground formation anomalies.).

ANALOGY IN THE CHEMICAL ARTS

See, for example, *Ex parte Bland*, 3 USPQ2d 1103 (Bd. Pat App. & Inter. 1986) (Claims were drawn to a particulate composition useful as a preservative for an animal foodstuff (or a method of inhibiting fungus growth in an animal foodstuff therewith) comprising verxite having absorbed thereon propionic acid. All references were concerned with absorbing biologically active materials on carriers, and therefore the teachings in each of the various references would have been pertinent to the problems in the other references and the invention at hand.); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983) (Problem confronting inventor was preventing electrostatic buildup in PTFE tubing caused by hydrocarbon fuel flow while precluding leakage of fuel. Two prior art references relied upon were in the rubber hose art, both referencing the problem of electrostatic buildup caused by fuel flow. The court found that because PTFE and rubber are used by the same hose manufacturers and experience the same and similar problems, a solution found for a problem experienced with either PTFE or rubber hosing would be looked to when facing a problem with the other.); *In re Mlot-Fijalkowski*, 676 F.2d 666, 213 USPQ 713 (CCPA 1982) (Problem faced by appellant was enhancement and immobilization of dye penetrant indications. References which taught the use of dyes and finely divided developer materials to produce colored images preferably in, but not limited to, the duplicating paper art were properly relied upon because the court found that appellant's problem was one of dye chemistry, and a search for its solution would include the dye arts in general.).

ANALOGY IN THE MECHANICAL ARTS

See, for example, *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992) (Applicant claimed an improvement in a hose clamp which differed from the prior art in the presence of a preassembly "hook" which maintained the preassembly condition of the clamp and disengaged automatically when the clamp

was tightened. The Board relied upon a reference which disclosed a hook and eye fastener for use in garments, reasoning that all hooking problems are analogous. The court held the reference was not within the field of applicant's endeavor, and was not reasonably pertinent to the particular problem with which the inventor was concerned because it had not been shown that a person of ordinary skill, seeking to solve a problem of fastening a hose clamp, would reasonably be expected or motivated to look to fasteners for garments. The Commissioner further argued in the brief on appeal that a disengageable catch is a common everyday mechanical concept, however the court held that the Commissioner did not explain why a "catch" of unstated structure is such a concept, and why it would have made the claimed invention obvious.). Compare *Stevenson v. International Trade Comm.*, 612 F.2d 546, 550, 204 USPQ 276, 280 (CCPA 1979) ("In a simple mechanical invention a broad spectrum of prior art must be explored and it is reasonable to permit inquiry into other areas where one of ordinary skill in the art would be aware that similar problems exist.").

Also see *In re Deminski*, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986) (Applicant's claims related to double-acting high pressure gas transmission line compressors in which the valves could be removed easily for replacement. The Board relied upon references which taught either a double-acting piston pump or a double-acting piston compressor. The court agreed that since the cited pumps and compressors have essentially the same function and structure, the field of endeavor includes both types of double-action piston devices for moving fluids.); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 227 USPQ 766 (Fed. Cir. 1985) (Claims at issue were directed to an instrument marker pen body, the improvement comprising a pen arm holding means having an integrally molded hinged member for folding over against the pen body. Although the patent owners argued the hinge and fastener art was nonanalogous, the court held that the problem confronting the inventor was the need for a simple holding means to enable frequent, secure attachment and easy removal of a marker pen to and from a pen arm, and one skilled in the pen art trying to solve that problem would have looked to the fastener and hinge art.); and *Ex parte Goodyear Tire & Rubber Co.*, 230 USPQ 357 (Bd. Pat. App. & Inter. 1985) (A reference in the clutch art was held reasonably pertinent to the friction problem faced by applicant, whose claims were directed to a braking material, because brakes and clutches utilize interfacing materials to accomplish their respective purposes.).

ANALOGY IN THE ELECTRICAL ARTS

See, for example, *Wang Laboratories, Inc. v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993) (Patent claims were directed to single in-line memory modules (SIMMs) for installation on a printed circuit motherboard for use in personal computers. Reference to a SIMM for an industrial controller was not necessarily in the same field of endeavor as the claimed subject matter merely because it related to memories. Reference was found to be in a different field of endeavor because it involved memory circuits in which modules of varying sizes may be added or replaced, whereas the claimed invention involved compact modular memories. Furthermore, since memory modules of the claims at issue were intended for personal computers and used dynamic random-access-memories, whereas reference SIMM was developed for use in large industrial machine controllers and only taught the use of static random-access-memories or read-only-memories, the finding that the reference was nonanalogous was supported by substantial evidence.); *Medtronic, Inc. v. Cardiac Pacemakers*, 721 F.2d 1563, 220 USPQ 97 (Fed. Cir. 1983) (Patent claims were drawn to a cardiac pacemaker which comprised, among other components, a runaway inhibitor means for preventing a pacemaker malfunction from causing pulses to be applied at too high a frequency rate. Two references disclosed circuits used in high power, high frequency devices which inhibited the runaway of pulses from a pulse source. The court held that one of ordinary skill in the pacemaker designer art faced with a rate-limiting problem would look to the solutions of others faced with rate limiting problems, and therefore the references were in an analogous art.).

EXAMPLES OF ANALOGY IN THE DESIGN ARTS

See MPEP § 1504.03 for a discussion of the relevant case law setting forth the general requirements for analogous art in design applications.

For examples of analogy in the design arts, see *In re Rosen*, 673 F.2d 388, 213 USPQ 347 (CCPA 1982) (The design at issue was a coffee table of contemporary styling. The court held designs of contemporary furniture other than coffee tables, such as the desk and circular glass table top designs of the references relied upon, would reasonably fall within the scope of the knowledge of the designer of ordinary skill.); *Ex parte Pappas*, 23 USPQ2d 1636 (Bd. Pat. App. & Inter. 1992) (At issue was an ornamental design for a feed bunk with an inclined corner configuration. Examiner relied upon references to a bunk lacking the inclined corners claimed by appellant and the *Architectural Precast Concrete Drafting Handbook*. The Board found the *Architectural Precast Concrete Drafting Handbook* was analogous art, noting that a bunk may be a wood or concrete trough, and that both references relied upon "disclose structures in which at least one upstanding leg is generally perpendicular to a base portion to define a corner configuration between the leg and base portion."); *In re Butera*, 1 F.3d 1252, 28 USPQ2d 1399 (Fed. Cir. 1993) (unpublished - not citable as precedent) (The claimed invention, a spherical design for a combined insect repellant and air freshener, was rejected by the Board as obvious over a single reference to a design for a metal ball anode. The court reversed, holding the reference design to be nonanalogous art. "A prior design is of the type claimed if it has the same general use as that claimed in the design patent application . . . . One designing a combined insect repellant and air freshener would therefore not have reason to know of or look to a design for a metal ball anode." 28 USPQ2d at 1400.).

2141.02 Differences Between Prior Art and Claimed Invention

Ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole. See MPEP § 2111 - § 2116.01 for case law pertaining to claim interpretation.

THE CLAIMED INVENTION AS A WHOLE MUST BE CONSIDERED

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (Claims were directed to a vibratory testing machine (a hard-bearing wheel balancer) comprising a holding structure, a base structure, and a supporting means which form "a single integral and gaplessly continuous piece." *Nortron* argued the invention is just making integral what had been made in four bolted pieces, improperly limiting the focus to a structural difference from the prior art and failing to consider the invention as a whole. The prior art perceived a need for mechanisms to dampen resonance, whereas the inventor eliminated the need for dampening via the one-piece gapless support structure. "Because that insight was contrary to the understandings and expectations of the art, the structure effectuating it would not have been obvious to those skilled in the art." 713 F.2d at 785, 218 USPQ at 700 (citations omitted).).

See also *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) (Claims were directed to a three step process for preparing sweetened foods and drinks. The first two steps were directed to a process of producing high purity maltose (the sweetener), and the third was directed to adding the maltose to foods and drinks. The parties agreed that the first two steps were unobvious but formed a known product and the third step was obvious. The Solicitor argued the preamble was directed to a process for preparing foods and drinks sweetened mildly and thus the specific method of making the high purity maltose (the first two steps in the claimed process) should not be given weight, analogizing with product-by-process claims. The court held "due to the admitted unobviousness of the first two steps of the claimed combination of steps, the subject matter as a whole would not have been obvious to one of ordinary skill in the art at the time the invention was made." 535 F.2d at 69, 190 USPQ at 17 (emphasis in original). The preamble only recited the purpose of the process and did not limit the body of the claim. Therefore, the claimed process was a three step process, not the product formed by two steps of the process or the third step of using that product.).

wherein, among other steps, the memory at each supermarket would identify coupons by manufacturer and transmit the data to a central computer to provide an audit thereby eliminating the need for clearinghouses and preventing retailer fraud. In challenging the propriety of an obviousness rejection, appellant argued he discovered the source of a problem (retailer fraud and manual clearinghouse operations) and its solution. The court found appellant's specification did not support the argument that he discovered the source of the problem with respect to retailer fraud, and that the claimed invention failed to solve the problem of manual clearinghouse operations.).

DISCLOSED INHERENT PROPERTIES ARE PART OF "AS A WHOLE" INQUIRY

"In determining whether the invention as a whole would have been obvious under 35 U.S.C. 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question... but also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification. . . Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention *as a whole,* and not some part of it, which must be obvious under 35 U.S.C. 103." *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977) (emphasis in original) (citations omitted) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The court found the invention as a whole was the ratio of 0.12 and its inherent property that the claimed devices maximized treatment capacity regardless of other variables in the devices. The prior art did not recognize that treatment capacity was a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable.").

Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). See MPEP § 2112 for the requirements of rejections based on inherency.

PRIOR ART MUST BE CONSIDERED IN ITS ENTIRETY, INCLUDING DISCLOSURES THAT TEACH AWAY FROM THE CLAIMS

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (Claims were directed to a process of producing a porous article by expanding shaped, unsintered, highly crystalline poly(tetrafluoroethylene) (PTFE) by stretching said PTFE at a 10% per second rate to more than five times the original length. The prior art teachings with regard to unsintered PTFE indicated the material does not respond to conventional plastics processing, and the material should be stretched slowly. A reference teaching rapid stretching of conventional plastic polypropylene with reduced crystallinity combined with a reference teaching stretching unsintered PTFE would not suggest rapid stretching of highly crystalline PTFE, in light of the disclosures in the art that teach away from the invention, i.e., that the conventional polypropylene should have reduced crystallinity before stretching, and that PTFE should be stretched slowly.).

2141.03 Level of Ordinary Skill in the Art [R-1]

FACTORS TO CONSIDER IN DETERMINING LEVEL OF ORDINARY SKILL

"Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applica-

ble to the pertinent art." *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (The Board disagreed with the examiner's definition of one of ordinary skill in the art (a doctorate level engineer or scientist working at least 40 hours per week in semiconductor research or development), finding that the hypothetical person is not definable by way of credentials, and that the evidence in the application did not support the conclusion that such a person would require a doctorate or equivalent knowledge in science or engineering.).

References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. *Ex parte Erlich*, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992).

SPECIFYING A PARTICULAR LEVEL OF SKILL IS NOT NECESSARY WHERE THE PRIOR ART ITSELF REFLECTS AN APPROPRIATE LEVEL

If the only facts of record pertaining to the level of skill in the art are found within the prior art of record, the court has held that an invention may be held to have been obvious without a specific finding of a particular level of skill where the prior art itself reflects an appropriate level. *Chore-Time Equipment, Inc. v. Cumberland Corp.*, 713 F.2d 774, 218 USPQ 673 (Fed. Cir. 1983). >See also *Okajima v. Bourdeau*, 261 F.3d 1350, 1355, 59 USPQ2d 1795, 1797 (Fed. Cir. 2001).<

ASCERTAINING LEVEL OF ORDINARY SKILL IS NECESSARY TO MAINTAIN OBJECTIVITY

"The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991). The examiner must ascertain what would have been obvious to one of ordinary skill in the art at the time the invention was made, and not to the inventor, a judge, a layman, those skilled in remote arts, or to geniuses in the art at hand. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 218 USPQ 865 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

2142 Legal Concept of *Prima Facie* Obviousness

The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. It allocates who has the burden of going forward with production of evidence in each step of the examination process. See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Saunders*, 444 F.2d 599, 170 USPQ 213 (CCPA 1971); *In re Tiffin*, 443 F.2d 394, 170 USPQ 88 (CCPA 1971), *amended*, 448 F.2d 791, 171 USPQ 294 (CCPA 1971); *In re Warner*, 379 F.2d 1011, 154 USPQ 173 (CCPA 1967), *cert. denied*, 389 U.S. 1057 (1968). The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. If, however, the examiner does produce a *prima facie* case, the burden of coming forward with evidence or arguments shifts to the applicant who may submit additional evidence of nonobviousness, such as comparative test data showing that the claimed invention possesses improved properties not expected by the prior art. The initial evaluation of *prima facie* obviousness thus relieves both the examiner and applicant from evaluating evidence beyond the prior art and the evidence in the specification as filed until the art has been shown to suggest the claimed invention.

To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be